**TABLE 1.** Patient Characteristics (Overall, $n = 109$)

| | Total | UIP Pattern, *n* (%) | Non-UIP Pattern, *n* (%) | *p* |
|---|---|---|---|---|
| No. of patients | 109 | 69 | 40 | |
| Gender | | | | 0.117 |
| Male | 103 | 67 (97) | 36 (90) | |
| Female | 6 | 2 (3) | 4 (10) | |
| Age (yr), median (range) | 69 (54–84) | 70 (55–84) | 69 (54–80) | 0.245 |
| Smoking status | | | | 0.763 |
| Never smoker | 0 | 0 | 0 | |
| Ex-smoker | 47 | 29 (42) | 18 (45) | |
| Current smoker | 62 | 40 (58) | 22 (55) | |
| Performance status (ECOG) | | | | 0.150 |
| 0–1 | 94 | 62 (90) | 32 (80) | |
| 2–3 | 15 | 7 (10) | 8 (20) | |
| Histology | | | | 0.723 |
| Adenocarcinoma | 36 | 22 (32) | 14 (35) | |
| Squamous cell carcinoma | 33 | 21 (30) | 11 (28) | |
| SCLC | 33 | 20 (29) | 13 (32) | |
| Others | 8 | 6 (9) | 2 (5) | |
| Clinical stages | | | | 0.044 |
| IIIA and B | 44 | 34 (49) | 10 (25) | |
| IV | 57 | 31 (45) | 26 (65) | |
| Recurrence after surgical resection | 8 | 4 (6) | 4 (10) | |
| SCLC | | | | 0.314 |
| Limited disease | 11 | 8 (40) | 3 (23) | |
| Extensive disease | 22 | 12 (60) | 10 (77) | |

UIP, usual interstitial pneumonia; SCLC, small cell lung cancer; ECOG, Eastern Cooperative Oncology Group.

**TABLE 2.** Incidence of Cytotoxic Chemotherapy-Related Exacerbation of ILD

| | No. of Patients (%) | | | |
|---|---|---|---|---|
| | Total, *n* (%) | UIP Pattern, *n* (%) | Non-UIP Pattern, *n* (%) | *p* |
| Overall | 109 | 69 | 40 | |
| Exacerbation of ILD | 24 (22) | 21 (30) | 3 (8) | 0.005 |
| ≥ Grade 3 | 22 (20) | 20 (29) | 2 (5) | 0.003 |
| Grade 3 | 5 (5) | 4 (6) | 1 (3) | |
| Grade 4 | 10 (9) | 10 (14) | 0 | |
| Grade 5 | 7 (6) | 6 (9) | 1 (3) | |

UIP, usual interstitial pneumonia; ILD, interstitial lung disease.

**TABLE 3.** Cytotoxic Chemotherapy Agents Considered to Cause the Exacerbation of ILD

| | UIP Pattern | | Non-UIP Pattern | |
|---|---|---|---|---|
| | No. of Patients Administered | Exacerbation of ILD (%) | No. of Patients Administered | Exacerbation of ILD (%) |
| Cisplatin | 21 | 2 (10) | 21 | 1 (5) |
| Carboplatin | 40 | 5 (13) | 19 | 0 |
| Paclitaxel | 31 | 1 (3) | 14 | 0 |
| Docetaxel | 25 | 7 (28) | 12 | 1 (8) |
| Etoposide | 21 | 5 (24) | 10 | 0 |
| Vinorelbine | 13 | 0 | 6 | 0 |
| Gemcitabine | 7 | 3 (43) | 10 | 1 (10) |
| S-1 | 7 | 2 (29) | 7 | 1 (14) |
| Irinotecan | 6 | 2 (33) | 6 | 0 |
| Amrubicin | 4 | 0 | 6 | 0 |
| Pemetrexed | 2 | 1 (50) | 1 | 0 |

UIP, usual interstitial pneumonia; ILD, interstitial lung disease.

($p = 0.044$), there were no significant differences in patient characteristics between both groups.

## Incidence of Cytotoxic Chemotherapy-Related Exacerbation of ILD

Of the 109 patients with ILD, 24 (22%) developed cytotoxic chemotherapy-related exacerbation of ILD. In particular, patients with UIP pattern developed cytotoxic chemotherapy-related exacerbation of ILD more frequently than those with non-UIP pattern (30 versus 8%, $p = 0.005$; Table 2). In addition, the incidence of grade 3 or worse pneumonitis/pulmonary infiltrates was significantly higher in patients with UIP pattern than in patients with non-UIP pattern (29 versus 5%, $p = 0.003$). Almost all of the patients who developed grade 3 or worse pulmonary toxicities received corticosteroid therapy. Nevertheless, 9% of the patients with UIP pattern died because of exacerbation of ILD, whereas 3% of those with non-UIP pattern died.

The median time from last administration of cytotoxic chemotherapy to the diagnosis of the exacerbation of ILD was 17 days (range: 0–25 days). The incidence rate of exacerbation of ILD is shown in Table 3 for each agent; docetaxel (28%) or etoposide (24%) frequently led to exacerbation of ILD for patients with UIP pattern. On the other hand, the incidence of exacerbation of ILD was relatively low for vinorelbine or paclitaxel. Cisplatin or carboplatin was mainly administered with another agent, and it was difficult to assess the risk for ILD. In patients with SCLC, 63% of exacerbation of ILD occurred during the first-line chemotherapy, whereas in patients with non-small cell lung cancer (NSCLC) the corresponding proportion was 31%. In addition, only one patient received further chemotherapy after exacerbation of ILD.

## The Risk of Cytotoxic Chemotherapy-Related Exacerbation of ILD

The results of the univariate analysis of risk factors for cytotoxic chemotherapy-related exacerbation of ILD are shown in Table 4. UIP pattern on CT was significantly associated with the exacerbation of ILD ($p = 0.005$). Multivariate analyses were performed using three variables (age, performance status, and CT pattern), and the results demonstrated that age (<70 years) (odds ratio [OR]: 2.75, 95% confidence interval: 1.03–7.93) and CT pattern (UIP) (OR:

**TABLE 4.** Univariate Analysis of Risk Factors Associated with Cytotoxic Chemotherapy-Related Exacerbation of ILD

| | No. of Patients | | | |
|---|---|---|---|---|
| | Overall | Ex of ILD | Non-Ex of ILD | *p* |
| No. of patients | 109 | 24 | 85 | |
| Gender | | | | — |
| Male | 103 | 24 | 79 | |
| Female | 6 | 0 | 6 | |
| Age (yr) | | | | 0.0897 |
| <70 | 56 | 16 | 40 | |
| ≥70 | 53 | 8 | 45 | |
| ECOG-PS | | | | 0.7043 |
| 0–1 | 94 | 20 | 74 | |
| 2–3 | 15 | 4 | 11 | |
| Histology | | | | 0.7119 |
| NSCLC | 76 | 16 | 60 | |
| SCLC | 33 | 8 | 25 | |
| CT pattern | | | | 0.0054 |
| UIP | 69 | 21 | 48 | |
| Non-UIP | 40 | 3 | 37 | |
| Stage | | | | 0.3186 |
| IIIA and B | 44 | 7 | 37 | |
| IV | 57 | 14 | 43 | |
| Recurrence after surgical resection | 8 | 3 | 5 | |

UIP, usual interstitial pneumonia; Ex, exacerbation; ILD, interstitial lung disease; PS, performance status; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group.

**TABLE 5.** Multivariate Analysis of Risk Factors Associated with Cytotoxic Chemotherapy-Related Exacerbation of ILD

| Variable | Odds Ratio | 95% CI | *p* |
|---|---|---|---|
| Age (<70 yr) | 2.75 | 1.03–7.93 | 0.0495 |
| ECOG-PS (2 and 3) | 2.20 | 0.51–8.74 | 0.2653 |
| CT pattern (UIP) | 6.98 | 2.04–33.79 | 0.0053 |

PS, performance status; CT, computed tomography; UIP, usual interstitial pneumonia; ECOG, Eastern Cooperative Oncology Group.

6.98, 95% confidence interval: 2.04–33.79) were significant independent risk factors (Table 5).

## Overall Survival

In this analysis, the median follow-up duration was 10.3 months. In SCLC, OS from the start of first-line chemotherapy was significantly shorter in patients with UIP pattern than those with non-UIP pattern (median OS: 9 versus 16 months, $p = 0.048$), whereas there was no significant difference in patients with NSCLC (median OS: 11 versus 9 months, $p = 0.334$).

## DISCUSSION

In patients with IPF, the incidence of lung cancer is reported to be higher than in patients without IPF,[9–13] and IPF has been recognized to be an independent risk factor for lung carcinogenesis.[11] There are some reports that patients with lung cancer with preexisting ILD or pulmonary fibrosis have a high risk of developing exacerbation after anticancer therapy,[3,16–18] and the incidence of exacerbation of ILD was 20 to 24%.[16,17] It is very important to establish an optimal treatment, which is considered to be safe and effective, for patients with lung cancer with ILD or IPF.

To our knowledge, this is the first study to evaluate the risk of cytotoxic chemotherapy-related ILD based on pretreatment chest CT patterns. In clinical practice, patients with lung cancer with ILD have been carefully treated with cytotoxic chemotherapy. Nevertheless, it is unknown what type of ILD has a high risk for exacerbation of ILD. In this study, patients with lung cancer with UIP pattern on CT findings demonstrated a high risk of exacerbation of ILD, compared with those with non-UIP pattern. This result suggests that chest CT patterns could be a risk factor for the development of chemotherapy-related exacerbation of ILD. Although age (<70 years) was also shown to be a risk factor, these patients might tend to receive multiple drugs for longer periods than elderly patients.

As there have been few reports about chemotherapy for patients with lung cancer with ILD, the optimal agent remains controversial. From Japan, a prospective study to evaluate the safety and efficacy of weekly paclitaxel in combination with carboplatin for advanced NSCLC with IIPs was reported.[19] One of 18 patients enrolled in this prospective study developed exacerbation of IIPs. Our study also showed that carboplatin and paclitaxel were relatively safe for patients with lung cancer with ILD, for whom this regimen might be one of the optimal regimens for those patients. Our results suggested that vinorelbine might also be relatively safe for patients with ILD. Nevertheless, we could not completely rule out the influence of biopsy for lung cancer diagnosis, before chemotherapy and before radiotherapy. It is known that the long-term survival in IPF shows poor prognosis compared with non-IPF, such as nonspecific interstitial pneumonia and other subgroups of IIPs.[1] In this study, although the UIP pattern on CT was significantly associated with the exacerbation of ILD, in patients with NSCLC with UIP pattern OS was not significantly different from those with non-UIP pattern. On the other hand, OS was significantly shorter in patients with SCLC with UIP pattern than in those with non-UIP pattern, and the type of ILD might influence the prognosis of patients with SCLC with ILD. Sixty-three percent of exacerbation of ILD in patients with SCLC occurred during the first-line chemotherapy, and they could not receive subsequent chemotherapy. On the other hand, approximately 70% of exacerbation of ILD in patients with NSCLC occurred during the second or subsequent line of chemotherapy and completed first-line chemotherapy. Thus, the rate of failure in first-line chemotherapy might contribute to poor prognosis in SCLC.

A major limitation of this retrospective analysis was that the diagnosis of ILD was based on CT findings and not on histologic diagnosis. In addition, the diagnosis of exacerbation of ILD was also based on CT findings, and we could not confirm histologically the exacerbation of ILD. Although we tried to exclude infection by bacteriological examination

and heart failure by physical examination or echocardiography, we cannot completely exclude pulmonary infection, pulmonary embolism, or heart failure. Nevertheless, their clinical and radiological courses were consistent with exacerbation of ILD. It was reported that in clinical practice, surgical lung biopsies were performed in 8 to 12% of patients,[20] and the ATS/ERS consensus statement also described criteria for the clinical diagnosis of IPF.[7] Moreover, the ability of high-resolution computed tomography scanning to diagnose IPF has reported sensitivities of 43 to 78% and specificities of 90 to 97% for confident radiological diagnosis.[21–25] Thus, we consider that it is appropriate to diagnose IPF using the clinical and radiological findings in clinical practice. Further studies are needed to clarify the relationship between the radiological patterns and pathological patterns of ILD for patients with lung cancer.

In conclusion, our study indicated that in patients with lung cancer with UIP pattern on CT findings, the risk of exacerbation of ILD was significantly higher than in those with non-UIP pattern. In particular, greater care is required when administering cytotoxic chemotherapy agents for patients with lung cancer with UIP pattern on CT findings.

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ORIGINAL ARTICLE

# Patterns of recurrence and outcome in patients with surgically resected small cell lung cancer

**Shizu Ogawa · Yoshitsugu Horio · Yasusi Yatabe · Takayuki Fukui · Simon Ito · Yoshinori Hasegawa · Tetsuya Mitsudomi · Toyoaki Hida**

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**Abstract**
*Background* Although prophylactic cranial irradiation (PCI) in limited-stage (LS) small cell lung cancer (SCLC) patients who are surgically resected and treated with adjuvant chemotherapy is considered to be a reasonable treatment option, the efficacy of PCI for those patients remains unclear.
*Methods* The records of 28 patients with SCLC undergoing curative surgery at the Aichi Cancer Center Hospital between 1995 and March 2008 were retrospectively reviewed to assess patterns of relapse and overall survival.
*Results* The patients were 27 men and 1 woman. Eight patients underwent induction chemotherapy. Fourteen patients (50%) had pathologic stage (p-stage) I disease, 7 patients (25%) had p-stage II, and 7 patients (25%) had p-stage III. Nineteen patients underwent adjuvant chemotherapy and one patient received adjuvant chemoradiotherapy. There were a total of 13 deaths and 8 were disease-related. Most patients developed hematogenous distant metastases before their death. The 5-year overall probability of survival was 47%. Ten (36%) of the 28 patients had a relapse. Two had a local relapse alone, one patient had combined local and distant relapses, and seven patients had distant metastases alone as their first site of failure. Four patients with p-stage II/III disease developed brain metastases with a cumulative incidence at 1 and 2 years of 25 and 36%, respectively.
*Conclusions* Our retrospective study suggested that PCI might have a role in surgically resected patients with p-stage II/III SCLC because of their relatively high frequency of brain metastasis.

**Keywords** Cranial irradiation · Metastasis · Small cell lung cancer · Thoracic surgery

S. Ogawa · Y. Horio (✉) · T. Hida
Department of Thoracic Oncology, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681, Japan
e-mail: yhorio@aichi-cc.jp

S. Ogawa · Y. Hasegawa
Department of Respiratory Medicine, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan

Y. Yatabe
Department of Pathology, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681, Japan

T. Fukui · S. Ito · T. Mitsudomi
Department of Thoracic Surgery, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681, Japan

## Introduction

Lung cancer is a leading cause of cancer mortality in the United States and in Japan [1, 2]. Lung cancer consists of two main histologic types; small cell lung cancer (SCLC) accounting for about 15% of lung cancer and non-SCLC (NSCLC) [3]. Concurrent chemoradiation therapy and prophylactic cranial irradiation (PCI) for limited stage (LS)-SCLC results in 5-year survival for approximately 25% of patients [4], and chemotherapy with platinum and etoposide or with CPT-11 only results in 5-year survival for fewer than 1% of patients with extensive stage (ES)-SCLC [5]. Because of its aggressive nature, for example rapid growth and early dissemination in lymph nodes, bones, adrenal glands, liver, and brain, the efficacy of surgery for treatment of SCLC is regarded as very limited [6], although it has been established by publications in the 1970s and early 1980s which showed long-term survival in

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surgically treated early stage patients [7]. At present, surgery plus adjuvant chemotherapy is standard of care for patients with clinical stage (c-stage) I SCLC [8].

At the time of initial diagnosis, 10–14% of patients with SCLC have detectable brain metastases and at the time of death [9] approximately one-third of patients harbor clinically recognized brain metastases, and over 50% of patients have brain metastases at postmortem examination [10]. The risk of central nervous system metastasis developing 2 years after successful treatment of SCLC has been reported to be approximately 35–65% [11]. A meta-analysis of the efficacy of PCI in 987 SCLC patients revealed a 25.3% decrease in cumulative incidence of brain metastasis at 3 years after PCI and an absolute increase in overall survival of 5.4% at 3 years [12]. Although this study included 140 patients with ES-SCLC, PCI has traditionally been limited to patients with LS-SCLC after meaningful response from combined-modality treatment has been achieved. However, recent results from a randomized study provide evidence that PCI not only reduces the incidence of symptomatic brain metastases but also prolongs disease-free and overall survival in patients with ES-SCLC [13]. Consequently, PCI is recommended for patients with limited-stage disease and extensive-stage disease who achieve a complete or near complete response to treatment, and can be considered for patients with a partial response to initial therapy even in ES-SCLC.

However, there is limited information about the frequency of brain failure in patients with early LS-SCLC who underwent surgery with adjuvant chemotherapy. The issue whether all patients with LS-SCLC undergoing surgery should receive PCI remains unclear. So, in this study, we reviewed our surgical results for 28 patients with LS-SCLC in our institution to see the relapse patterns, the frequency of brain metastasis and overall survival.

## Patients and methods

### Patients

Approval for this study was obtained from, and the need for individual patient consent was waived by, the institutional review board. Between 1995 and March 2008, twenty-eight patients with SCLC underwent surgery with nodal resection at the Department of Thoracic Surgery of Aichi Cancer Center Hospital. We collected complete clinical data for all patients, none of whom was lost to follow up.

### Histological diagnosis

For histological diagnosis patients were subjected to bronchoscopic biopsy or cytology and/or CT-guided biopsy. For 5 of 28 patients (18%), histological or cytological diagnosis was not obtained preoperatively. Preoperative diagnosis of SCLC was achieved for 10 patients only. For the remaining 13 patients, the preoperative diagnosis was large-cell neuroendocrine carcinoma (LCNEC) in three cases, adenocarcinoma in three cases, squamous cell carcinoma in three cases, carcinoma in two cases, NSCLC in one case, and large-cell carcinoma in one case. The histology of all the surgical resection specimens was reviewed. In all cases, diagnosis by light microscopy was confirmed by immunohistochemical methods. Histologic classification was performed according to the World Health Organization classification [14]. The postoperative diagnosis was SCLC in 15 cases and combined SCLC in 13 cases.

### Diagnostic workup

Standard diagnostic workup for all patients consisted in X-ray of the chest and thoracic and abdominal computed tomography (CT), bronchoscopy, brain magnetic resonance imaging (MRI) or CT, and bone scintigraphy or positron emission tomography (PET). Mediastinoscopy was not done. We used the TNM classification system of the International Union Against Cancer in this study [15], because precise staging and discrimination between choices of different options of treatment were required for surgical approach for these selected LS-SCLC patients. Pretreatment c-stages were IA, 15 patients; IB, 6 patients; IIA, 2 patients; IIB, 3 patients; IIIA, 2 patients.

### Treatment

Eight patients underwent induction chemotherapy. Among these, three patients with c-stage II/III disease who were preoperatively diagnosed as NSCLC on biopsy, received induction chemotherapy consisting of platinum (CDDP or carboplatin) and taxane (paclitaxel or docetaxel). Four patients with c-stage I SCLC and one patient with c-stage II SCLC consented to our in-house clinical procedure and received induction chemotherapy consisting of platinum and etoposide. Twenty-one patients received adjuvant treatment, and seven patients were not treated with adjuvant chemotherapy because of poor general condition ($n = 1$), refusal to consent ($n = 3$), and old age ($n = 3$). Nineteen patients underwent adjuvant chemotherapy consisting of platinum and etoposide or CPT-11. One double-cancer patient with pT1N1 SCLC and advanced hypopharynx cancer simultaneously received chemoradiotherapy consisting of CDDP plus 5-FU and intensity-modulated radiation therapy (IMRT: 66 Gy). One patient underwent adjuvant chemoradiotherapy consisting of CDDP plus etoposide and concurrent thoracic RT (42 Gy).

Survival was determined by use of the institutional database, which is updated with an annual institutional census or with each patient visit.

### Statistical analysis

Statistical analysis was carried out using SPSS software (SPSS, Chicago, IL, USA). Overall survival of patients from the time of operation was estimated by means of the Kaplan–Meier method. The cumulative incidence of brain metastasis was also calculated. Patients suffering progression at non-central nervous system sites and/or death from any cause were considered censored.

## Results

### Patient characteristics

From January 1995 to March 2008, a total of 28 patients underwent complete resection for SCLC. Baseline characteristics of patients according to the postoperative diagnosis are listed in Table 1. Twenty-seven were men and 1 was a woman. The median age of patients was 64.5 years (range 41–77). All patients had a history of cigarette smoking. No patient had a central tumor. Preoperative diagnosis of SCLC was made in 36% ($n = 10$) of 28 patients; postoperative diagnosis of combined SCLC was made in 15% ($n = 2$) of 13 patients (Table 1). Among 7 patients with c-stage II/III disease, 6 cases were preoperatively diagnosed as NSCLC on biopsy. Eight patients underwent induction chemotherapy. Three patients with c-stage II/III disease whose preoperative diagnosis was NSCLC received chemotherapy with platinum and taxane. One patient with c-stage II SCLC and four patients with c-stage I SCLC received induction chemotherapy consisting of platinum and etoposide. All patients underwent lobectomy with mediastinal lymph node dissection.

There was no perioperative death. Regarding pathologic stage, 13 patients had IA disease, 1 patient had IB, 4 patients had IIA, 3 patients had IIB, 5 patients had IIIA, and 2 patients had IIIB. Postoperatively, 21 patients received adjuvant treatment and 7 patients were not treated with adjuvant chemotherapy because of poor general condition ($n = 1$), patient refusal ($n = 3$), or old age ($n = 3$). Nineteen patients underwent adjuvant chemotherapy and one patient received chemoradiotherapy (Table 1). One patient with pT1N1SCLC and advanced hypopharynx cancer simultaneously received chemoradiation therapy consisting of CDDP plus 5-FU and intensity-modulated radiation therapy (66 Gy). Relationship between pretreatment clinical stages and postoperative pathologic stages is shown in Table 2. Because of inaccuracy of clinical staging, clinical understaging rate was approximately 36% (10/28), although 8 patients received induction therapy.

**Table 1** Demographics, clinical characteristics, and perioperative treatment of patients

| | Postoperative diagnosis | | |
|---|---|---|---|
| | Total ($n = 28$) | SCLC ($n = 15$) | Combined SCLC ($n = 13$) |
| Age (years) | | | |
| Median | 64.5 | 64 | 65 |
| Range | 41–77 | 54–77 | 41–77 |
| Sex | | | |
| Male | 27 | 14 | 13 |
| Female | 1 | 1 | 0 |
| Clinical stage | | | |
| I | 21 | 12 | 9 |
| II | 5[a,b] | 3 | 2 |
| III | 2[a] | 0 | 2 |
| Pathologic stage | | | |
| I | 14 | 8 | 6 |
| II | 7 | 4 | 3 |
| III | 7 | 3 | 4 |
| Preoperative diagnosis | | | |
| SCLC | 10 | 8 | 2 |
| LCNEC | 3 | 1 | 2 |
| Sq | 3 | 2 | 1 |
| Ad | 3 | 1 | 2 |
| La | 1 | 0 | 1 |
| NSCLC | 1 | 0 | 1 |
| Carcinoma | 2 | 1 | 1 |
| Tumor not diagnosed | 5 | 2 | 3 |
| Induction therapy | | | |
| Platinum + etoposide | 5 | 5 | 0 |
| Platinum + taxane | 3 | 0 | 3 |
| Adjuvant therapy | | | |
| Platinum + etoposide | 12 | 10 | 2 |
| CDDP + etoposide + RT | 1 | 1 | 0 |
| Platinum + CPT-11 | 7 | 1 | 6 |
| CDDP + 5-FU + RT | 1[c] | 1 | 0 |

[a] Six cases of seven patients with clinical stage II/III disease were preoperatively diagnosed as NSCLC on biopsy

[b] One patient who was preoperatively diagnosed as SCLC received induction CDDP plus etoposide chemotherapy followed by surgery and two course of adjuvant chemotherapy

[c] One patient with advanced hypopharynx cancer and pT1N1 SCLC underwent chemoradiotherapy with CDDP + 5-FU + RT

### Patient outcome

The median follow-up was 41.6 months (interquartile range 25.6–57.3) for all patients and 57.3 months (interquartile range 28.9–79.3) for those still alive. No patients

dropped out of the follow-up during the study period. The median survival for all patients was 59.2 months and the 5-year overall probability of survival was 47% (Fig. 1). Five-year survival for patients with c-stage I ($n = 21$), c-stage II ($n = 5$), and c-stage III disease ($n = 2$) were 53, 0, and 100%, respectively (Fig. 2). Five-year survival for patients with p-stage I ($n = 14$), p-stage II ($n = 7$), and p-stage III disease ($n = 7$) were 64, 25, and 43%, respectively (Fig. 3). There was no significant difference in survival among c-stages ($p = 0.08$, log-rank test) and between patients with p-stage I disease and those with p-stage II disease ($p = 0.35$, log-rank test). Despite small sample size, there were significant differences in survival between patients with p-stage I disease and those with p-stage III disease ($p = 0.04$, log-rank test). Overall survival did not differ significantly between patients with combined SCLC and those with SCLC ($p = 0.91$, log-rank test) (Fig. 4).

Ten (36%) of the 28 patients had a relapse (Table 3). Among these patients, two had a local relapse alone, one patient had combined local and distant relapses, and the other seven patients had distant metastases alone as their first site of failure. Nine patients relapsed within 2 years after surgery. Median relapse-free survival for all patients was 52.5 months (95%CI 16.6, N/A). There was no obvious difference in relapse pattern between patients with combined SCLC and those with SCLC. Four patients with p-stage II/III disease developed brain metastases with a cumulative incidence at 1 and 2 years of 25 and 36%, respectively (Fig. 5). One patient with p-stage III disease developed brain metastasis concurrently with liver and bone metastases. The other patient with p-stage III disease and two patients with p-stage II disease had brain metastases as the only site of first recurrence. There were a total of 13 deaths and 8 were disease-related. Most patients

**Table 2** Relationship between clinical and pathologic stages

| Clinical stage | Pathologic stage | | |
|---|---|---|---|
| | I | II | III |
| I | 12 (3) | 4 (1) | 5 |
| II | 1 (1) | 3 (1) | 1 (1) |
| III | 1 (1) | 0 | 1 |

Numbers in parentheses are the numbers of patients who received induction therapy

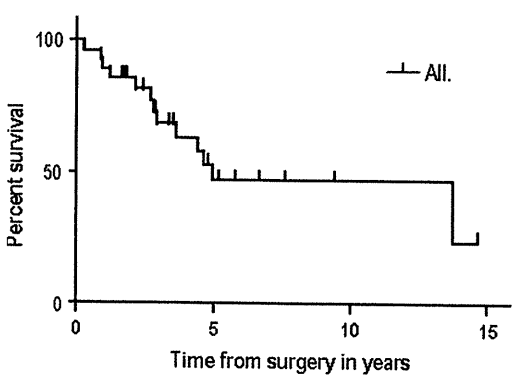


**Fig. 1** Survival curve for patients with resected SCLC

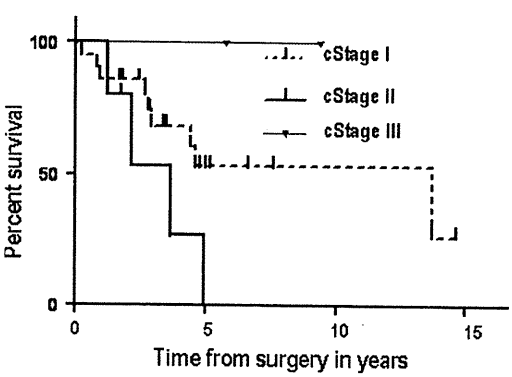


**Fig. 2** Survival curves for patients with resected SCLC by clinical stages

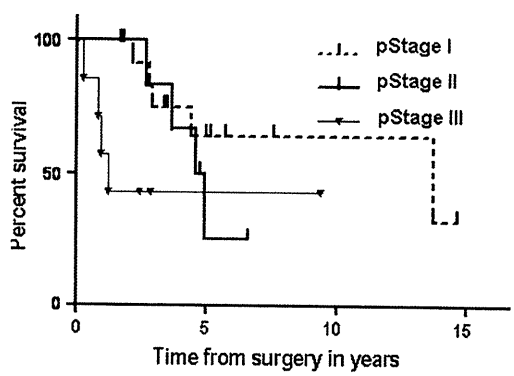


**Fig. 3** Survival curves for patients with resected SCLC by pathologic stages

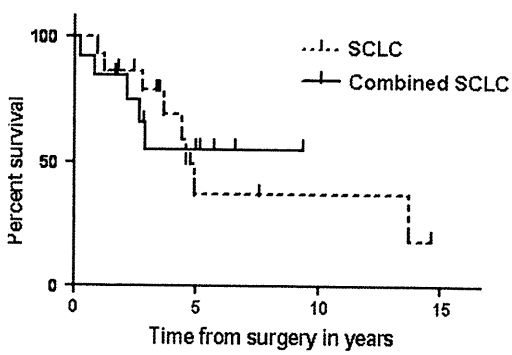


**Fig. 4** Survival curves for patients with resected SCLC according to histologic subtypes

**Table 3** Site of the first relapse by pathologic and clinical stages

| Variables | Overall | p-Stage I | p-Stage II | p-Stage III | c-Stage I | c-Stage II | c-Stage III |
|---|---|---|---|---|---|---|---|
| No. of patients | 28 (15) | 14 (8) | 7 (4) | 7 (3) | 21 (12) | 5 (3) | 2 (0) |
| No. of recurrences | 10 (6) | 3 (1)[a] | 4 (3) | 3 (2)[b] | 5 (3)[a,b] | 5 (3) | 0 |
| Recurrence | | | | | | | |
| Local | | | | | | | |
| Mediastinum | 3 (1) | 2 (1)[a] | 0 | 1 | 2 (1)[a] | 1 | 0 |
| Distant | | | | | | | |
| Brain | 4 (3) | 0 | 3 (2) | 1 (1)[b] | 2 (2)[b] | 2 (1) | 0 |
| Bone | 3 (3) | 1 (1)[a] | 0 | 2 (2)[b] | 2 (2)[a,b] | 1 (1) | 0 |
| Liver | 2 (2) | 1 (1)[a] | 0 | 1 (1)[b] | 2 (2)[a,b] | 0 | 0 |
| Lung | 1 | 1 | 0 | 0 | 1 | 0 | 0 |
| Adrenal gland | 1 (1) | 0 | 1 (1) | 0 | 0 | 1 (1) | 0 |

Numbers in parentheses are the number of patients with postoperative diagnosis of SCLC

[a] One patient with clinical and pathological stage I disease developed local relapse concurrently with liver and bone metastases

[b] One patient with clinical stage I and pathological stage III disease developed brain metastasis simultaneously with liver and bone metastases

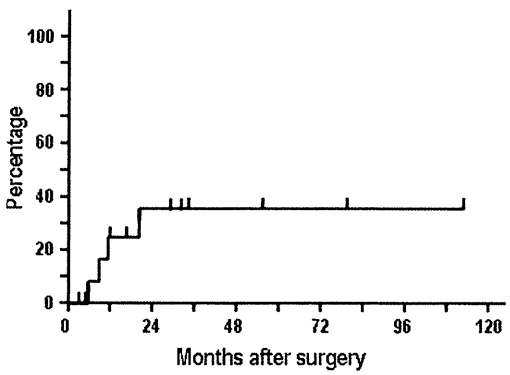


**Fig. 5** Cumulative incidence of brain metastasis in patients with p-stages II/III disease

developed hematogenous distant metastases before their deaths.

## Discussion

The prognosis of resected SCLC is considered to be poorer than that of surgically treated NSCLC. Vallieres et al. [16] has reported that 5-year survival of surgically treated LS-SCLC patients was approximately 50% for p-stage I disease, approximately 40% for p-stage II, and approximately 15% for p-stage III. A Japanese large-scale registry study reported that 5-year survival of resected SCLC patients was approximately 60% for p-stage I disease, approximately 40% for p-stage II, and approximately 30% for p-stage III [17]. In our study, the 5-year probability of survival was 64% for p-stage I disease, 25% for p-stage II, 43% for p-stage III. Our results are almost similar to those of the Japanese study.

Because of its aggressive nature, for example rapid growth and early dissemination in lymph nodes, bones, adrenal glands, liver, and brain, the role of surgery in treatment of SCLC is considered to be very limited [6]. SCLC usually occurs centrally, and typical initial radiographic images show a larger hilar mass with bulky mediastinal lymphadenopathy. Thus, SCLC for indication of surgical resection which often arises peripherally is relatively rare [7]. In fact, a large-scale registry study from Japan reported that there were a few SCLC patients (3%) among 13010 lung cancer patients who underwent surgery at the certified teaching hospitals in 1999 [17]. Although patients with very limited SCLC (cT1-2N0) basically proceed to surgical resection, there are several other situations in which surgery can be useful [18]. One situation is surgery for confirmation of diagnosis. Another situation is surgery for patients with preoperative diagnosis of resectable NSCLC. A third situation is improvement of local control in the combination treatment with chemotherapy and radiotherapy, because for patients with combined histology tumors, for example combined SCLC, the NSCLC component is less sensitive to chemotherapy and radiotherapy. Surgery for these situations may contribute to prolonged survival for undiagnosed lung cancer and T1-3N1-2 SCLC. In our study, histological or cytological diagnosis was not achieved preoperatively for 5 of 28 patients, and preoperative diagnosis of SCLC was achieved for 10 patients only. Furthermore, approximately half (13) of 28 patients had combined SCLC histology.

Recurrence in the brain is associated with substantial morbidity and mortality in SCLC [13]. Because of high risk of brain metastasis after diagnosis of SCLC, PCI has been studied in an attempt to treat and control metastatic brain tumors before clinical manifestation. The benefit of PCI is

greatest for patients with LS-SCLC and ES-SCLC who have complete or near complete response to treatment [12]. However, use of PCI after combined-modality treatment with surgery for resectable LS-SCLC has not yet been investigated sufficiently. As far as we are aware, only 2 Japanese studies have reported the frequency of brain relapse after surgery for LS-SCLC [19, 20]. One Japanese multi-institutional phase II study (JCOG9101) has reported that recurrence after surgery occurred in 43% (26/61) of patients overall, in 29% (10/35) of patients with p-stage I disease, in 50% (4/8) of patients with p-stage II, and in 67% (12/18) of patients with p-stage III, and that the incidence of brain metastasis was 15% (9/61) in patients overall, 11% (4/35) in patients with p-stage I disease, 38% (3/8) in patients with p-stage II, and 11% (2/18) in patients with p-stage III [20]. Another Japanese study showed that relapse after surgery occurred in 34 of 69 (49%) patients who underwent complete resection of SCLC and in 27% (8/30) of patients with p-stage I disease, 58% (7/12) of patients with p-stage II, 69% (18/26) of patients with p-stage III, and 100% (1/1) of patients with p-stage IV [19]. In this report, the frequency of brain relapse as a first relapse site was reported to be 7% (2/30) for patients with p-stage I disease, 25% (3/12) for patients with p-stage II, 27% (7/26) for patients with p-stage III, and 100% (1/1) for patients with p-stage IV. Combined results from our study and from two other Japanese studies revealed that brain metastases as first site of failure developed in 26 (16%) of the total of 158 patients who underwent surgery for LS-SCLC, in 6 (8%) of 79 patients with p-stage I disease, 8 (30%) of 27 patients with p-stage II, and 11 (22%) of 51 patients with p-stage III. For LS-SCLC patients treated with chemoradiation therapy, the frequency of brain metastasis as the first recurrence site has been reported to be 37% [21]. In addition, as for the role of PCI for treatment of NSCLC, the risk of brain metastasis has been reported to be 17% (71/422) for patients with stage III NSCLC treated with chemoradiation therapy [22]. Thus, although it is unclear whether PCI after combined modality treatment with surgery for resectable LS-SCLC could improve survival, PCI may be beneficial at least for patients with p-stage II/III disease to reduce the incidence of brain metastasis, although a randomized study is necessary.

The principal role of PCI is to prevent brain failure and to reduce its frequency, and to improve survival [13]. Surgically treated patients with p-stage I SCLC are the most favorable subset in SCLC. Combined results from our study and two other Japanese studies revealed that brain metastases as first site of failure developed in only 8% (6/79) of patients with p-stage I SCLC. It has been reported that in adjuvant trasuzumab studies of breast cancer PCI would not be justified by a frequency of less than 5% in incidence of brain metastasis [23]. In this regard, very early LS-SCLC, for example p-stage I disease, would be excluded from candidates for PCI, because of low frequency of brain relapse.

Our retrospective study suggested that PCI might be suitable for surgically resected patients with p-stage II/III SCLC to reduce the incidence of brain metastasis, although a randomized study is necessary. It is likely that very early LS-SCLC, for example p-stage I disease would be excluded from candidates for PCI.

**Acknowledgments** This work was supported in part by a Grant-in-Aid from the Japan Society for Promotion of Science, and a grant from the Aichi Cancer Research Foundation to Y Horio.

**Conflict of interest** The authors declare no conflicts of interest.

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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-

Thoracic Oncology Division, National Cancer Center Hospital East, Japan
Received for publication June 25, 2010; Accepted for publication November 1, 2010
Correspondence to Dr. Koichi Suyama, ksuyama@east.ncc.go.jp

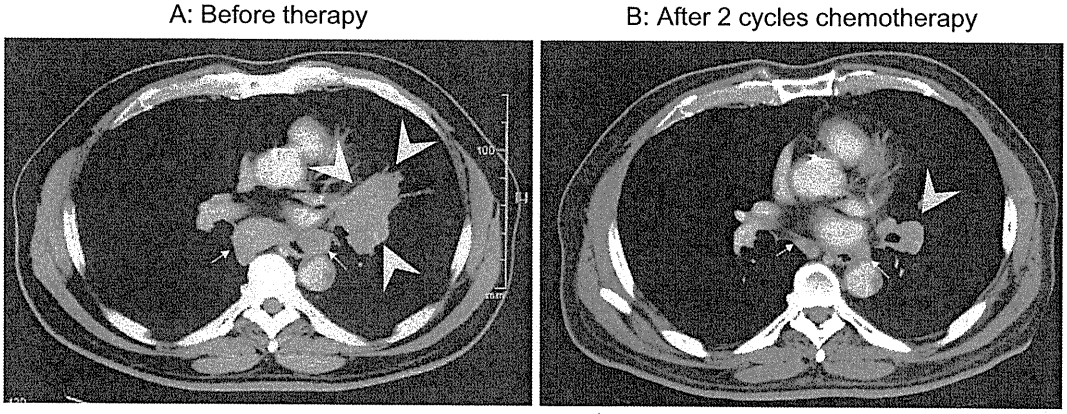
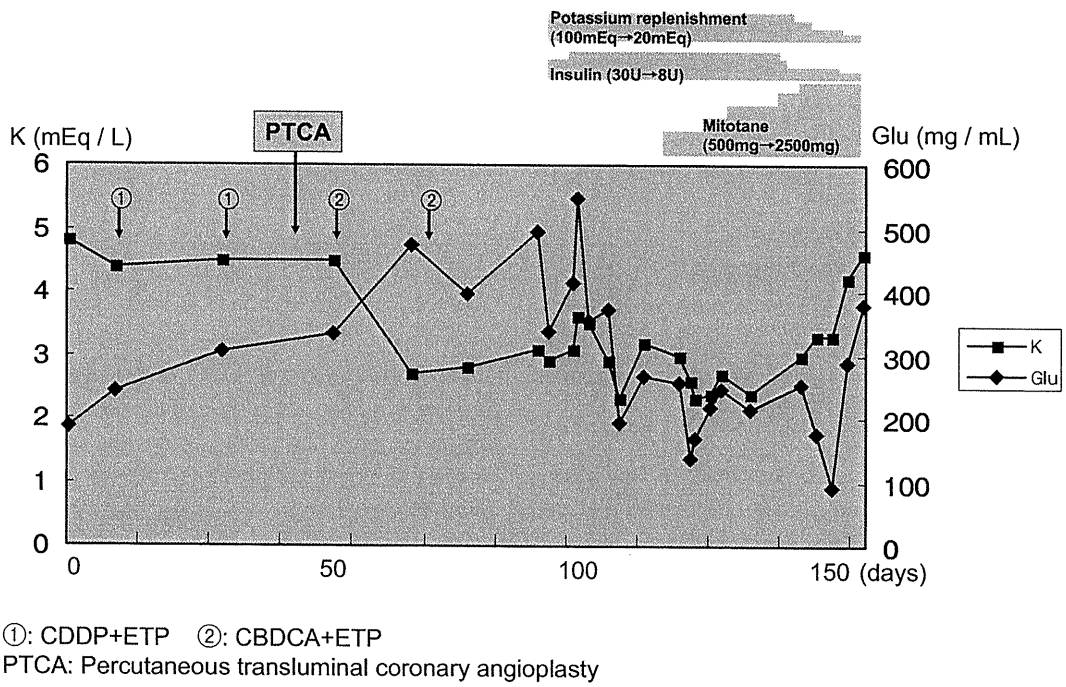



**Figure 1. A: Computed tomography (CT) image obtained before chemotherapy. A chest CT revealed a mass in the left hilum of the lung (arrowhead) and mediastinal lymph node swelling (arrow). B: CT image obtained after 2 cycles of chemotherapy. The main tumor and swollen lymph node show signs of reduction.**




①: CDDP+ETP ②: CBDCA+ETP
PTCA: Percutaneous transluminal coronary angioplasty

**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

*Seiji Niho, MD,* Kaoru Kubota, MD,* Kiyotaka Yoh, MD,* Koichi Goto, MD,* Hironobu Ohmatsu, MD,* Keiji Nihei, MD,† Yuichiro Ohe, MD,* and Yutaka Nishiwaki, MD**

**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.

Divisions of *Thoracic Oncology and †Radiation Oncology, National Cancer Center Hospital East, Chiba, Japan.

Disclosure: The authors declare no conflicts of interest.

Address for correspondence: Seiji Niho, MD, Division of Thoracic Oncology, National Cancer Center Hospital East, Kashiwanoha 6-5-1, Kashiwa, Chiba 277-8577, Japan. E-mail: siniho@east.ncc.go.jp



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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.

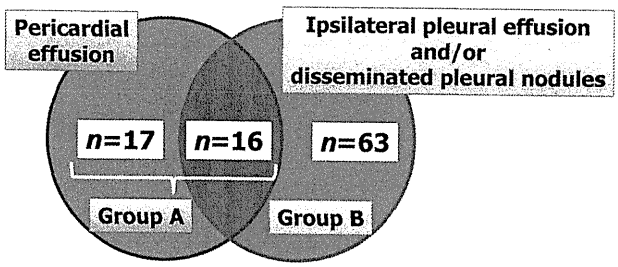


**FIGURE 1.** Patients with small cell lung cancer with M1a. Group A included patients with pericardial effusion, and group B included patients with ipsilateral pleural effusion or disseminated pleural nodules, but without pericardial effusion.

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

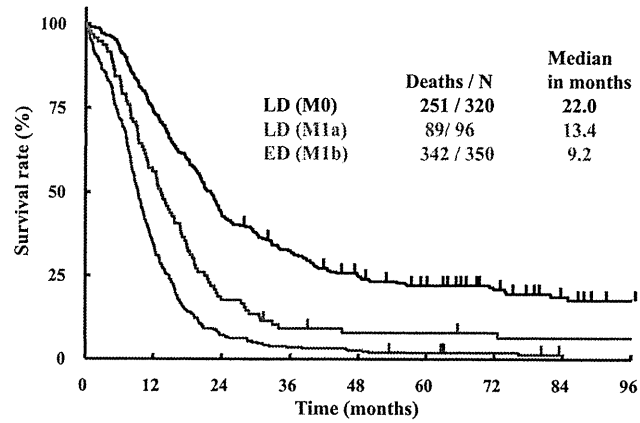


**FIGURE 2.** Overall survival among all 766 patients with M-category small cell lung cancer. LD, limited disease; ED, extensive disease.

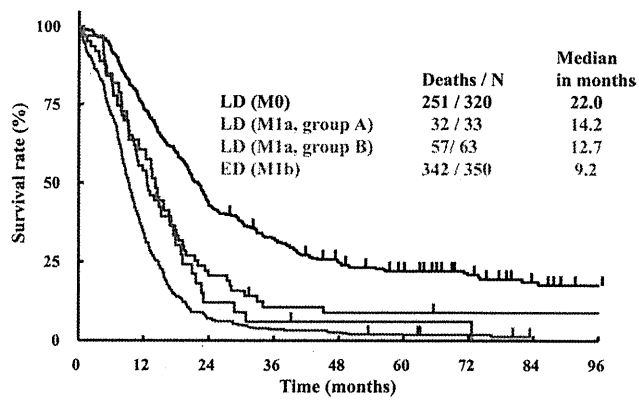


**FIGURE 3.** Overall survival among patients with M-category small cell lung cancer, subgroups A and B. LD, limited disease; ED, extensive disease.

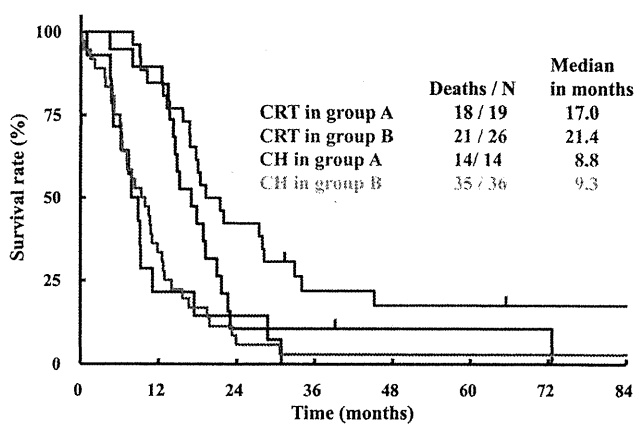


**FIGURE 4.** Overall survival among M1a patients with small cell lung cancer according to subgroups A, B, and initial treatment delivered. CRT, chemoradiotherapy; CH, chemotherapy.

**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.

## ACKNOWLEDGMENTS

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Clinical Medicine Insights: Oncology



REVIEW

# Review of the Management of Relapsed Small-Cell Lung Cancer with Amrubicin Hydrochloride

Tatsuo Kimura, Shinzoh Kudoh and Kazuto Hirata

Department of Respiratory Medicine, Graduate School of Medicine, Osaka City University, 1-4-3 Asahi-machi, Abeno-ku, Osaka 545-8585, Japan. Corresponding author email: kimutats@med.osaka-cu.ac.jp

**Abstract:** Lung cancer is the leading cause of cancer death, and approximately 15% of all lung cancer patients have small-cell lung cancer (SCLC). Although second-line chemotherapy can produce tumor regression, the prognosis is poor. Amrubicin hydrochloride (AMR) is a synthetic anthracycline anticancer agent and a potent topoisomerase II inhibitor. Here, we discuss the features of SCLC, the chemistry, pharmacokinetics, and pharmacodynamics of AMR, the results of *in vitro* and *in vivo* studies, and the efficacy and safety of AMR monotherapy and combination therapy in clinical trials. With its predictable and manageable toxicities, AMR is one of the most attractive agents for the treatment of chemotherapy-sensitive and -refractory relapsed SCLC. Numerous studies are ongoing to define the applicability of AMR therapy for patients with SCLC. These clinical trials, including phase III studies, will clarify the status of AMR in the treatment of SCLC.

**Keywords:** amrubicin, amrubicinol, topoisomerase II inhibitor, sensitive relapse, refractory relapse, second-line chemotherapy

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## Small-Cell Lung Cancer

Lung cancer is the leading cause of cancer death, and approximately 15% of all patients with lung cancer are diagnosed with small-cell lung cancer (SCLC). After an apparently successful frontline therapy, most patients experience recurrence because of intrinsic or acquired resistance. At the time of recurrence, many SCLC patients are potential candidates for further therapy. Although second-line chemotherapy has been shown to cause tumor regression, many responders do not live long.[1] The median survival time (MST) is rarely more than 12 months and is usually less than 6 months after second-line therapy.[2] Treatment options for patients with recurrent SCLC include monotherapies of etoposide (VP-16),[3] oral VP-16,[4] teniposide,[5] vinorelbine,[6,7] irinotecan,[8] paclitaxel,[9] gemcitabine,[10,11] pemetrexed,[12,13] picoplatin,[14] topotecan,[15] etc.; combination therapies of VP-16 and cisplatin (CDDP),[16] doxorubicin+paclitaxel,[17] carboplatin (CBDCA)+paclitaxel,[18] CBDCA+irinotecan (CPT-11),[19] CDDP+CPT-11,[20] CPT-11+VP-16,[21] CPT-11+gemcitabine,[22] topotecan+CDDP,[23] vincristine+doxorubicin+cyclophosphamide,[24] VP-16+CDDP+ifosfamide,[25] paclitaxel+ifosfamide+CDDP,[26] CPT-11+CDDP+mitomycin,[27] etc.; or re-challenge with front-line chemotherapy.[16]

The response rate (RR) of recurrent SCLC to second-line chemotherapy, or to re-challenge with frontline chemotherapy, is highly dependent on the time between the completion of frontline chemotherapy and tumor recurrence. Patients who fail to respond to frontline chemotherapy or who relapse shortly after completion of frontline chemotherapy tend to have poor survivals, while patients who relapse 6 to 12 months after completion of frontline chemotherapy have RRs as high as 60% and better survivals.[28]

By analogy to chemo-sensitive cancers, including SCLC, two main categories of patients receiving second-line chemotherapy have been described: "chemotherapy-sensitive relapse" and "chemotherapy-refractory relapse". Chemotherapy-sensitive relapse patients have a frontline response that lasts more than 90 days after the completion of treatment. These patients receive the greatest benefit from second-line chemotherapy. In contrast, chemotherapy-refractory relapse patients comprise those who either did not respond to frontline chemotherapy, or responded initially but relapsed within 90 days of its completion.[29] New drugs are urgently needed to control SCLC more effectively, particularly for chemotherapy-refractory relapse patients.

## Anthracyclines: Doxorubicin, Epirubicin, and Amrubicin

Anthracyclines, such as daunorubicin and doxorubicin, are widely used in the treatment of a variety of cancers. However, the cumulative dose-limiting cardiotoxicity of doxorubicin is a major obstacle to its use,[30] and great efforts have been made to discover means of ameliorating, preventing and delaying this side-effect.

A major metabolic pathway of anthracyclines is the reduction of the C-13 carbonyl group to a hydroxyl group by carbonyl reductase.[31] This step is generally regarded as an inactivation, because the 13-hydroxyl metabolites of doxorubicin, epirubicin and daunorubicin are much less cytotoxic than the corresponding parental drugs, unlike idarubicinol and idarubicin, whose metabolites are equipotent.[32]

Amrubicin hydrochloride (AMR; (+)-(7S, 9S)-9-acetyl-9-amino-7-[(2-deoxy-b-D-erythro-pentopyranosyl)-oxy]-7,8,9,10-tetrahydro-6,11-dihydroxy-5,12-naphthacenedione hydrochloride) is a novel synthetic 9-aminoanthracycline derivative, with a structure similar to doxorubicin. (Fig. 1) AMR is currently approved for the treatment of SCLC and non-small-cell lung cancer (NSCLC) in Japan. Its antitumor activity was found to be superior to that of doxorubicin in experimental therapeutic models using human tumor xenografts.[33] In addition, AMR showed much less cardiotoxicity than doxorubicin in chronic experimental models using rabbits and dogs.[34,35]

Similar to other anthracyclines, AMR is metabolized to amrubicinol (AMR-OH), through reduction of its C-13 ketone group to a hydroxy group.[36] However, in contrast to other anthracyclines, the *in vitro* cytotoxic activity of AMR-OH is 18–220 times more potent than that of its parent compound, AMR.[31]

In mice experiments, Noguchi et al showed that AMR-OH has more potent antitumor activity than its parent compound, AMR.[37] The levels of AMR-OH in the tumors of these mice were higher than doxorubicin levels in doxorubicin-treated mice. In contrast, the levels of AMR and AMR-OH were lower than those of doxorubicin in several non-tumor