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ORIGINAL ARTICLE

Clinical impact of post-progression survival on overall survival in elderly patients with extensive disease small-cell lung cancer

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Keywords
Elderly; extensive disease small-cell lung cancer; overall survival; post-progression survival; progression-free survival.

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Abstract

Background: The effects of first-line chemotherapy on overall survival (OS) might be confounded by subsequent therapies in patients with small-cell lung cancer (SCLC). Therefore, the objective of our study was to determine the relationships between progression-free survival (PFS) or post-progression survival (PPS) and OS after first-line chemotherapy in elderly patients with extensive disease-SCLC (ED-SCLC), using individual level data.

Methods: Between July 1998 and December 2014, we analyzed 57 cases of elderly patients with ED-SCLC who were treated with carboplatin and etoposide as first-line chemotherapy. The relationships between PFS and PPS with OS were analyzed at an individual level.

Results: Spearman rank correlation and linear regression analyses showed that PPS was strongly correlated with OS ($r = 0.92$, $P < 0.05$, $R^2 = 0.83$) and PFS was moderately correlated with OS ($r = 0.76$, $P < 0.05$, $R^2 = 0.25$). The best response at second-line treatment and the number of regimens after progression beyond first-line chemotherapy were both significantly associated with PPS ($P < 0.05$).

Conclusions: PPS has a stronger impact on OS than PFS in elderly ED-SCLC patients after first-line chemotherapy. In addition, the response at second-line treatment and the number of additional regimens after first-line treatment are significant independent prognostic factors for PPS. These results suggest that OS in elderly ED-SCLC patients may be influenced by treatments subsequent to first-line chemotherapy; however, this remains to be verified with prospective studies.

Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide.[1] Neuroendocrine tumors account for approximately 20% of lung cancers; most of these (~15%) are small-cell lung cancer (SCLC).[2] Approximately 30% of SCLC patients have limited-stage disease SCLC (LD-SCLC), which is characterized by locoregional tumors in the hemithorax, mediastinum, or supraclavicular lymph nodes, while the remainder has extensive-stage disease SCLC (ED-SCLC).[3] In patients with ED-SCLC, chemotherapy alone can palliate symptoms and prolong survival in most patients; in chemoresponsive patients, prophylactic cranial irradiation (PCI) can also palliate symptoms and prolong survival. However, long-term survival is rare in patients with ED-SCLC.[4,5] The incidence of lung cancer increases with age. Although the median age at diagnosis is 70 years, elderly patients are underrepresented in clinical

trials.[6] The first-line treatment of choice in elderly ED-SCLC patients is four cycles of carboplatin plus etoposide.[2,7] Although many patients initially achieve clinical remission or disease control with first-line chemotherapy, most subsequently experience disease progression and eventually die of ED-SCLC. We examined first-line carboplatin and etoposide combination chemotherapy because it is considered the standard first-line chemotherapy in elderly ED-SCLC cases.[7] The median overall survival (OS) of patients with ED-SCLC is approximately one year. For elderly ED-SCLC patients, OS is shorter and options for subsequent chemotherapy are limited.

Progression-free survival (PFS) and OS are two common endpoints in cancer trials. OS is usually preferred, because it is reliable, precise, meaningful, and easily documented by noting the date of death. However, subsequent lines of therapy might confound the effect of first-line treatment on OS.[8] In contrast, PFS is quicker to measure, can be measured more conveniently, and, therefore, may be easier to assess than OS.[9] If there is a strong correlation between PFS and OS, then PFS may be a surrogate endpoint for OS. In non-small cell lung cancer (NSCLC), increases in PFS do not necessarily increase OS, but post-progression survival (PPS) is strongly associated with OS after first-line treatment.[10–12] Although PFS following first-line chemotherapy has not been validated as a surrogate endpoint for OS, PPS has been shown to be strongly associated with OS after first-line chemotherapy for advanced NSCLC in individual-level data.[13–15] Furthermore, it has been suggested that OS can be approximated as the sum of PPS and PFS.[8] A previous report demonstrated a strong correlation between PPS and OS after first-line chemotherapy using cisplatin plus irinotecan in non-elderly patients with ED-SCLC and good performance status (PS) using individual level data.[16] However, the relationship between PPS and OS is unknown in elderly ED-SCLC patients. The significance of PPS in elderly ED-SCLC patients also remains unclear at the level of the individual patient. Therefore, the objective of our study was to determine the relationships between PFS or PPS and OS after first-line chemotherapy in elderly patients with ED-SCLC using individual level data; the patients included in our study had limited options for subsequent-line chemotherapy. We also explored the prognostic values of baseline patient and tumor characteristics with respect to PPS.

Methods

Patients

Between July 1998 and December 2014, 59 elderly patients with ED-SCLC were treated with carboplatin and etoposide as first-line chemotherapy and were retrospectively enrolled in this study. The inclusion criteria were as follows: (i) histologically or cytologically confirmed SCLC; (ii) 70 years of age or older at the time of chemotherapy; (iii) Eastern Cooperative Oncology Group (ECOG) PS of 0–3 at the beginning of the first-line treatment; and (iv) disease recurrence after first-line treatment. The tumor response was not evaluated in two cases. These two patients were excluded from the analyses to maintain uniformity in patient background characteristics. Thus, data from 57 patients were analyzed. The study protocol was approved by the Institutional Review Board of Gunma Prefectural Cancer Center (405-27047) and was conducted in accordance with the Helsinki Declaration of 1964 (revised 2008). Because of the retrospective nature of this study, the need for informed consent was waived.

Treatments

The patients in this study were treated with carboplatin (area under the curve [AUC] = 5 on day 1, followed by a pause of 21 days) and etoposide (80 mg/m^2/day on days 1, 2, and 3, followed by a pause of 21 days). This cycle was repeated every three to four weeks for a maximum of four courses. After chemotherapy, prophylactic cranial irradiation (PCI; 25 Gy/10 fractions) was administered to patients with a complete or near-complete response, as shown by a scar-like shadow on chest computed tomography, if recommended by the treating physician.

Assessment of treatment efficacy

The best overall response was recorded as the tumor response. Radiographic tumor responses were evaluated according to Response Evaluation Criteria in Solid Tumors, version 1.1: complete response (CR), disappearance of all target lesions; partial response (PR), at least a 30% decrease in the sum of the target lesion diameters with the summed baseline diameters as a reference; progressive disease (PD), at least a 20% increase in the sum of the target lesion diameters with the smallest sum observed during the study serving as reference; and stable disease (SD), insufficient shrinkage to qualify as PR and insufficient expansion to qualify as PD.[17] PFS was calculated from the start of treatment to the date of PD or death from any cause. OS was recorded from the first day of treatment until death or was censored on the date of the last follow-up. PPS was recorded as the time from tumor progression until death or was censored on the date of the last follow-up.

Treatment-free interval

We analyzed patients according to treatment-free interval (TFI) because TFI is known to be a predictive factor of

second-line chemotherapy.[18,19] In this study, we defined the TFI as the period from the date of completion of first-line treatment to first relapse. When PCI was performed as first-line treatment, the date of completion of first-line treatment was defined as the last day of the treatment. In many trials, relapsed SCLC patients whose TFI was more than 90 days were defined as sensitive relapse. In this study, we also defined these patients as sensitive relapse.

Statistical analyses

To examine whether PFS or PPS was correlated with OS, we used Spearman rank correlation and linear regression analyses. In order to identify possible prognostic factors for PPS, the proportional hazards model with a stepwise regression procedure was applied. Hazard ratios (HR) and 95% confidence intervals (CI) were estimated using this model. Because HR is defined for a 1-unit difference, some factors were converted to an appropriately scaled unit. PPS values were compared using the log-rank test. A P value of ≤ 0.05 was considered significant for all tests. The two-tailed significance level was also set at 0.05. All statistical analyses were performed using JMP version 11.0 for Windows (SAS Institute, Cary, NC, USA).

Results

Patient characteristics and treatment efficacy

All of the 57 patients included in the analysis died. The median follow-up time was 5.3 months (range 0.3–89.5). The characteristics of the 57 patients (median age, 75 years; range 70–86) included in the present study are shown in Table 1. Target lesions were evaluated in all cases. None of the patients achieved CR, while 40 patients (70.1%) achieved PR, 5 (8.8%) achieved SD, and 12 (21.1%) achieved PD. The response rate was 70.1% and the disease control rate was 78.9%.

After progressing past first-line chemotherapy, 37 patients received subsequent chemotherapy, while the remaining 20 patients did not receive any further chemotherapy. Among the 57 patients, the median number of follow-up therapeutic regimens was 1 (range 0–3 regimens). The chemotherapy regimens employed, after progressing past the first-line chemotherapy regimen, are shown in Table 2. Amrubicin was the most common second-line chemotherapy agent, and topotecan was the most common third-line chemotherapy agent.

The median PFS and OS were 4.2 and 8.2 months, respectively (Fig 1).

Table 1 Baseline patient characteristics

Characteristic	
Gender	
Male/female	52/5
Median age at treatment (years)	75 (70–86)
Performance status	
0/1/2/≥ 3	6/28/18/5
Histology	
Small cell carcinoma/others	57/0
Smoking history	
Yes/no	57/0
Stage	
IIIB/IV	0/57
Number of first-line chemotherapy courses	
1/2/3/4/≥ 5	4/15/8/30/0
Median (range)	4 (1–4)
Number of regimens after progression following first-line chemotherapy	
0/1/2/3/≥ 4	20/26/10/1/0
Median (range)	1 (0–3)
Prophylactic cranial irradiation	
Yes/no	2/55
Type of relapse	
Sensitive/refractory	12/45
Median treatment-free interval, days (range)	92 (28–1201)

Table 2 Chemotherapy regimens employed after progression following first-line chemotherapy

Chemotherapy regimen	Second-line	≥third-line	Total
CBDCA + etoposide re-challenge	1	1	2
CBDCA + irinotecan	11	3	14
Amrubicin	21	2	23
Topotecan	4	6	10
Other	0	0	0

Relationship between overall survival (OS) and progression-free survival (PFS), and post-progression survival (PPS)

The relationship between OS and PFS, and PPS, respectively, is shown in Figure 2. PPS was strongly associated with OS ($r = 0.92$, $P < 0.05$, $R^2 = 0.83$), based on Spearman's rank correlation coefficient and linear regression, whereas PFS was moderately correlated with OS ($r = 0.76$, $P < 0.05$, $R^2 = 0.25$). The column graph between PFS and PPS in the overall population is shown in Figure 3.

Factors affecting PPS

Post-progression survival was strongly associated with OS. Therefore, the association between PPS and various clinical factors was assessed. In univariate analysis, the number of courses of first-line treatment administered, PS at the end of first-line treatment and at the beginning of

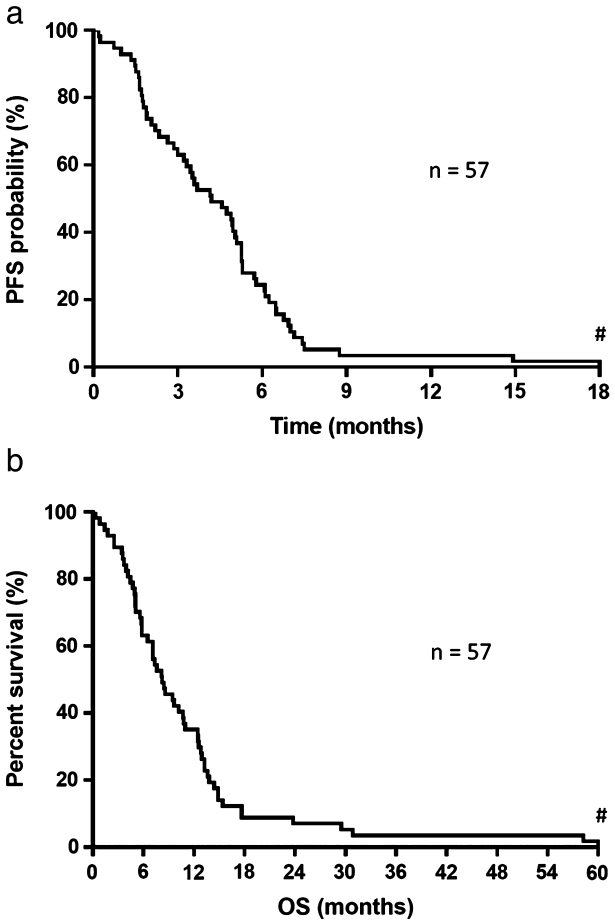

Figure 1 (**a**) Kaplan–Meier plots showing progression-free survival (PFS). Median PFS: 4.2 months. (**b**) Kaplan–Meier plots showing overall survival (OS). Median overall survival: 8.2 months. (#) There was 1 outlier in these data.

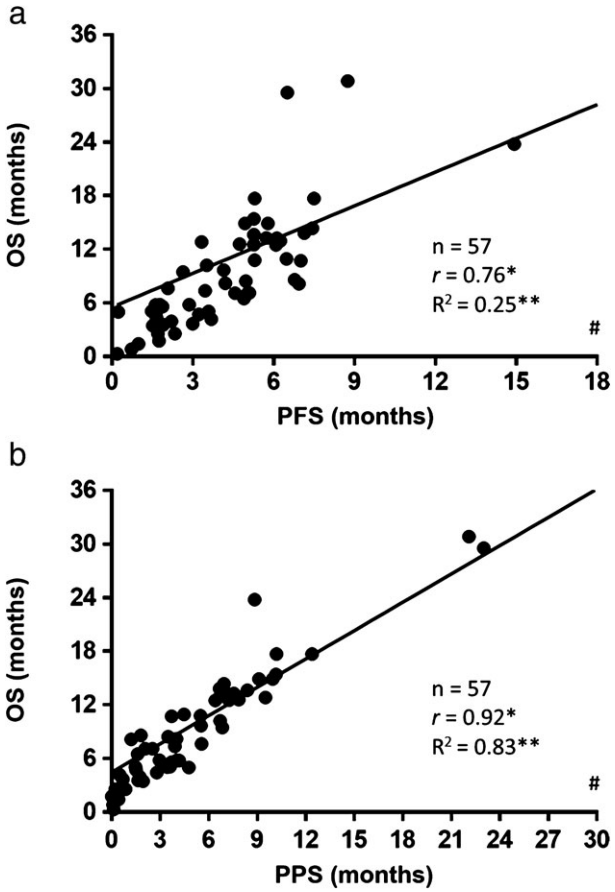

Figure 2 (**a**) Correlation between overall survival (OS) and progression-free survival (PFS). (**b**) Correlation between overall survival (OS) and post-progression survival (PPS). (#) There were 2 outliers in these data. *The *r* values represent Spearman's rank correlation coefficient. **The R^2 values represent linear regression.

second-line treatment, type of relapse (refractory/sensitive), the best responses at first-line and second-line treatment, and the number of regimens after progression beyond first-line chemotherapy were found to be associated with PPS ($P < 0.05$; Table 3). Multivariate analysis for PPS was then conducted, which revealed that the best response at second-line treatment (non-PD/PD) and the number of regimens after progression beyond first-line chemotherapy were significantly associated with PPS ($P < 0.05$; Table 4). The log-rank tests confirmed that PPS was significantly associated with the best response at second-line treatment (non-PD/PD) as well as the number of regimens employed after progression beyond first-line chemotherapy ($P < 0.05$; Fig 3). Based on the best response at second-line treatment, patients with non-PD had a median PPS of 7.8 months, which was longer than that of their counterparts, who had a median PD of 3.7 months (log-rank test, $P < 0.05$; Fig 4a). The median PPS for those who were not administered additional regimens after progression beyond first-line chemotherapy was 1.5 months; with 1 additional regimen, the median PPS was 4.4 months; and with ≥ 2 regimens, the median PPS was 8.3 months (log-rank test, $P < 0.05$; Fig 4b). These results remained consistent after adjustment using the Cox proportional hazards model (Table 4).

Discussion

We examined the relationships of OS with PFS and PPS at an individual level in elderly patients with ED-SCLC. PPS was strongly associated with OS, whereas PFS was moderately correlated with OS. In addition, the best response to second-line treatment (non-PD vs. PD), and the number of regimens employed after progression following first-line chemotherapy independently affected PPS. To our knowledge, this is the first report of individual-level factors that affect PPS for elderly ED-SCLC patients after first-line chemotherapy.

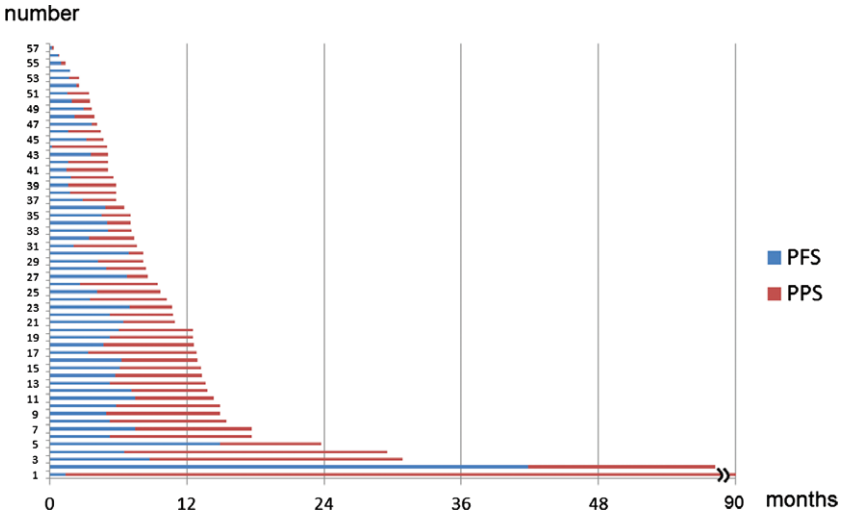

Figure 3 Progression-free survival (PFS) and post-progression survival (PPS) in the overall population.

The validity of surrogate endpoints has previously been determined through meta-analyses.[20,21] In recent years, biostatisticians have proposed a wide variety of measures for validating surrogate endpoints.[22,23] Although PFS is a potential surrogate endpoint for OS in ED-SCLC, its validity remains controversial.[24] As an alternative, Broglio *et al.* recently investigated PPS (which they referred to as survival post progression, defined as OS minus PFS) in simulated clinical trial settings under the assumption that treatment affected PFS but not PPS. They found that the length of the median PPS determines whether OS is a suitable endpoint in any particular trial.[8] Recently, PPS was found to be strongly associated with OS after first-line chemotherapy for advanced NSCLC in a clinical trial, and we have previously reported the significance of PPS for advanced NSCLC and extensive stage disease SCLC based on an analysis of individual patients.[11–16]

In contrast with the findings of a previous study, we did not observe that PFS was a surrogate endpoint for OS in elderly ED-SCLC cases, although PPS was not evaluated in the previous study.[24] We analyzed our results pertaining to first-line therapy, which suggested that PFS did not adequately reflect OS in such settings. We found that PFS was much shorter than PPS, and, thus, PPS was closely related to OS – the relationship was linear. The fact that PPS accounted for the majority of OS suggests that the chemotherapy used was not sufficiently effective for PFS to be a significant component of OS. Thus, in clinical trials where patients are expected to have a short PFS after first-line chemotherapy, for example, for those with ED-SCLC, as was the case in our study, factors that affect PPS need to be considered.

Based on trial-level data for advanced NSCLC, a long PPS is associated with a good PS and the use of first-line monotherapy, including a molecular targeted agent.[11] Studies based on individual advanced NSCLC patients revealed

Table 3 Univariate Cox regression analysis of baseline patient characteristics for post-progression survival

	Post-progression survival		
Factors	Hazard ratio	95% CI	*P*
Gender			
Male/female	0.69	0.49–3.30	0.46
Age (years) at the beginning of first-line treatment	0.99	0.92–1.06	0.89
PS at the beginning of first-line treatment	1.31	0.93–1.84	0.10
Number of courses of first-line treatment administered	0.71	0.53–0.95	**0.02**
Best response at first-line treatment			
PR/non-PR	0.51	0.28–0.95	**0.03**
Non-PD/PD	0.64	0.33–1.36	0.23
PS at the end of first-line treatment	2.21	1.69–2.87	**< 0.001**
Prophylactic cranial irradiation			
Yes/no	0.81	0.13–2.65	0.77
Type of relapse			
Refractory/sensitive	2.33	1.24–4.73	**< 0.001**
Age at the beginning of second-line treatment	0.97	0.88–1.06	0.51
PS at the beginning of second-line treatment	1.69	1.13–2.53	**0.01**
Best response at second-line treatment			
PR/non-PR	0.17	0.05–0.43	**< 0.001**
Non-PD/PD	0.14	0.05–0.34	**< 0.001**
Administration of AMR			
Yes/no	0.70	0.40–1.21	0.20
Administration of TOP			
Yes/no	0.68	0.32–1.31	0.26
Number of regimens after progression beyond first-line chemotherapy	0.38	0.25–0.57	**< 0.001**

Bold *P* values are statistically significant ($P < 0.05$). AMR, amrubicin; CI, confidence interval; PD, progressive disease; PR, partial response; PS, performance status; TOP, topotecan.

Table 4 Multivariate Cox regression analysis

Factors	Post-progression survival		
	Hazard ratio	95% CI	*P*
Best response at first-line treatment			
PR/non-PR	0.99	0.35–0.39	0.99
PS at the end of first-line treatment	1.30	0.59–2.88	0.50
Type of relapse			
Refractory/sensitive	0.80	0.32–3.39	0.64
PS at the beginning of second-line treatment	1.33	0.77–2.19	0.28
Best response at second-line treatment			
Non-PD/PD	0.18	0.06–0.53	**< 0.01**
Number of regimens after progression beyond first-line chemotherapy	0.49	0.22–0.99	**0.04**

Bold *P* values are statistically significant ($P < 0.05$). CI, confidence interval; PD, progressive disease; PR, partial response; PS, performance status.

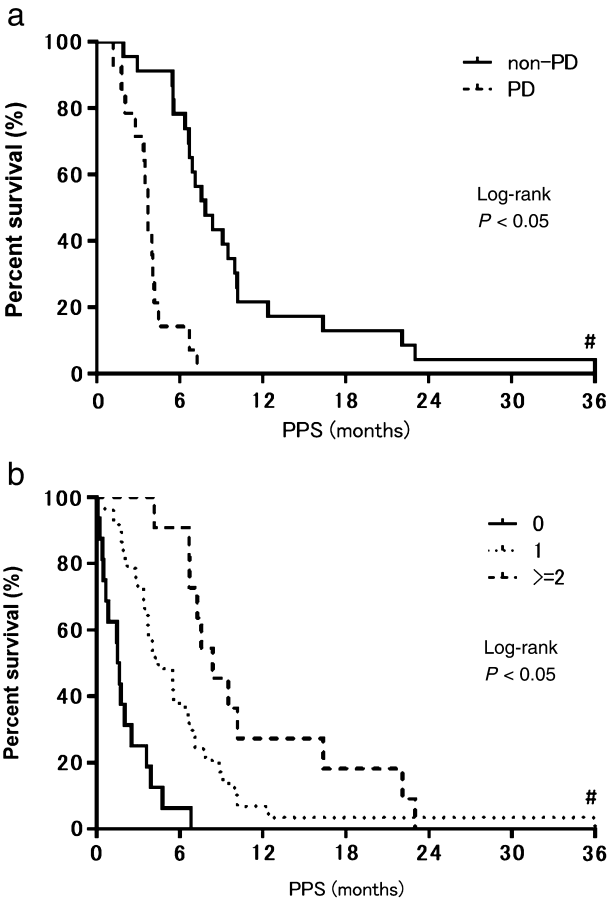

Figure 4 (**a**) Kaplan-Meier plots showing post-progression survival (PPS), according to the best response following second-line treatment. Non-progressive disease (non-PD), median = 7.8 months; progressive disease (PD), median = 3.7 months. (**b**) Kaplan–Meier plots showing post-progression survival (PPS), according to the number of regimens after progression. No further regimen, median = 1.5 months; 1 regimen, median = 4.4 months; ≥ 2 regimens, median = 8.3 months. (#) There was 1 outlier in these data.

that a long PPS was associated with PS at the beginning of second-line treatment, the best response at second-line treatment, and the number of regimens after disease progression beyond first-line chemotherapy.[13] Furthermore, studies based on individual ED-SCLC patients treated with cisplatin plus irinotecan revealed that a long PPS was associated with the best response at second-line treatment and the number of regimens after progression beyond first-line chemotherapy.[16] To date, however, no predictive factors for PPS in elderly ED-SCLC patients have been identified, hence the reason for, and the novelty of, our study. We found that the factors predictive of PPS in elderly ED-SCLC patients mirrored those previously observed in the general population, and confirmed the significance of these relationships using log-rank tests. The strong correlation between PPS and OS can be explained by the brief PFS period. Our findings suggest that patients in whom the disease has been controlled with second-line treatment achieve prolonged PPS after progression following first-line chemotherapy. These patients are also likely to be able to continue chemotherapy and achieve prolonged PPS, which is associated with a longer OS. The number of treatment regimens used after progression beyond first-line chemotherapy probably reflects the increasing number of available drugs, such as amrubicin, irinotecan, and topotecan, which are available as second-line or third-line chemotherapy for ED-SCLC. In fact, a number of different agents were used to treat our patients, as shown in Table 2.

This study has several limitations. First, the sample size was relatively small. However, because relatively few elderly ED-SCLC patients are treated with first-line carboplatin and etoposide at our institution, this limitation is difficult to overcome, especially as the patients needed to have similar background characteristics. Nevertheless, our institution treats the relatively largest number of such cases, and the practice policy is largely unified simply because this is a single institution. There is, of course, some bias, but understanding the nature of this bias ensures that the results are still meaningful. In a future study, we intend to include a larger patient cohort, and more detailed examination is warranted. Second, we could not thoroughly evaluate treatments after progression beyond second-line chemotherapy, although only a few patients received third-line or subsequent chemotherapy. Third, because different treating physicians documented patient responses, the timing of evaluation of PFS and tumor response rates may have been less accurate than if only a single physician had documented all responses. Fourth, chemotherapy regimens differ between Japan and the United States. Amrubicin is

an effective second-line chemotherapy drug for a number of cancers, including SCLC. In a phase III trial, it resulted in a significantly improved response rate compared with topotecan and also improved survival, especially in a subgroup of refractory patients.[25] On the basis of this trial, amrubicin is now the standard second-line chemotherapy agent for ED-SCLC in Japan.

In conclusion, PPS has a greater impact on OS than PFS in elderly ED-SCLC patients after first-line chemotherapy. In addition, the response at second-line treatment and the number of additional regimens after first-line treatment are significant independent prognostic factors for PPS. These results suggest that treatments subsequent to first-line chemotherapy in elderly ED-SCLC patients can affect OS. However, as this conclusion is based on a retrospective analysis, prospective studies are warranted to verify our results.

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Disclosure

No authors report any conflict of interest.

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