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ORIGINAL ARTICLE

The Clinical Impact of the Post-progression Survival on the Overall Survival in Elderly Patients or Those with a Poor Performance Status and Extensive-disease Small-cell Lung Cancer

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ABSTRACT —— ***Objective.*** The post-progression survival (PPS) following first-line chemotherapy has been shown to influence the overall survival (OS) of patients with malignant diseases, including lung cancer. The aim of this study was to compare the influence of the PPS on the OS of elderly or poor performance status (PS) patients with extensive-disease small-cell lung cancer (ED-SCLC) to that of the progression-free survival (PFS) on the OS. ***Methods.*** The medical records of patients with ED-SCLC who were elderly (≥70 years old) or had a poor PS and who received chemotherapy between March 2010 and December 2017 were retrospectively reviewed. Seventy-five such patients who were treated with carboplatin-based chemotherapy or amrubicin monotherapy as first-line intervention were included, and the relationships between the OS and the PFS and PPS were analyzed. ***Results.*** The median age of the 75 patients was 72 years old. The median PFS and OS intervals were 6.1 and 11.8 months, respectively. Spearman's rank correlation and linear regression analyses showed that the PPS was more strongly correlated with the OS ($r = 0.91$, $R^2 = 0.83$, $P = 0.0001$) than with the PFS ($r = 0.81$, $R^2 = 0.65$, $P = 0.017$). In the multivariate analysis, a good PS, using carboplatin-based chemotherapy as the first-line chemotherapy, achieving a response to first-line chemotherapy, and implementation of second-line chemotherapy were independent favorable predictors of the PPS. ***Conclusion.*** The PPS after first-line chemotherapy has a strong impact on the OS in elderly or poor PS patients with ED-SCLC. Given the findings of this study, the development of novel anti-cancer drugs that are effective against SCLC is warranted to improve the PPS in such patients.

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KEY WORDS —— Small-cell lung cancer, Elderly patients, Poor performance status, Post-progression survival

INTRODUCTION

Despite being one of the most chemosensitive solid tumor types, small-cell lung cancer (SCLC) has an extremely poor prognosis.[1] Most patients with SCLC experience relapse due to the emergence of drug-resistant tumor cells even after highly successful induction therapy.[2-4] Approximately 50% of all patients with SCLC in Japan are over 70 years of age,[5] and the Japan Lung Cancer Society recommends chemotherapy with carboplatin (CBDCA) plus etoposide (ETP) as the standard treatment modality for such elderly patients.[6]

We previously performed clinical studies showing that amrubicin (AMR) monotherapy is a viable treatment option for chemotherapy-naïve elderly patients or those with a poor performance status (PS) with extensive-disease (ED) SCLC,[7,8] suggesting that AMR monotherapy may be a feasible treatment option alongpan.

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side or in lieu of CBDCA plus ETP treatment. Despite the fact that many patients initially achieve clinical responses to first-line chemotherapy, most subsequently experience disease progression and eventually die of ED-SCLC.

The progression-free survival (PFS) and overall survival (OS) are commonly used endpoints in anti-cancer therapy trials. The OS is usually preferred because it is reliable and easily documented by noting the date of death. However, subsequent lines of chemotherapy may obscure the contribution of first-line treatment to the OS.[9] In contrast, the PFS is an earlier time point, can be measured more conveniently, and may thus be easier to assess than the OS.[10] However, previous studies have found the post-progression survival (PPS) to be strongly associated with the OS after first-line chemotherapy for advanced non-small-cell lung cancer (NSCLC), as did other studies of patients with advanced NSCLC and ED-SCLC.[11-15]

Despite these previous findings, the relationship between the PPS and OS is not sufficiently clear in patients with ED-SCLC. Accordingly, the significance of the PPS in elderly patients with ED-SCLC or those with a poor PS also remains unclear. Therefore, the aim of this study was to determine the relationship between the PPS and OS after first-line chemotherapy in elderly or poor-PS patients with ED-SCLC.

METHODS

Patient selection and data collection

The eligibility criteria for this retrospective study were as follows: histologically or cytologically proven SCLC; limited-disease (LD) or ED disease (as defined by the Union for International Cancer Control TNM classification, 7th edition); ≥70 years old or an Eastern Cooperative Oncology Group (ECOG) PS score ≥2; history of CBDCA-based combination therapy or AMR as first-line treatment at Kitasato University Hospital between March 2010 and December 2017; and measurable target lesions on imaging examinations by chest radiography, computed tomography (CT) of the chest and abdomen, or other procedures, such as magnetic resonance imaging (MRI) of the head, positron emission tomography (PET), or combined PET/CT imaging.

The treatment-free interval (TFI) is known to be a predictor of efficacy of second-line chemotherapy.[16,17] In this study, we defined the TFI as the period between the date of completion of first-line treatment and that of first relapse. In many trials, TFIs of ≥90 and <90 days are defined as sensitive and refractory relapse, respectively.

The study protocol was approved by the institutional ethics review board of Kitasato University Hospital. Informed consent was not required owing to the retrospective nature of the study.

Treatment

In clinical practice, the treatment regimen for ED-SCLC (i.e. a CBDCA-based regimen or AMR monotherapy) was selected at the discretion of the attending physician. Regimens based on CBDCA (area under the curve = 5 on day 1, followed by a pause of 21 days) or AMR monotherapy (35 or 40 mg/m^2 on days 1, 2, and 3, followed by a pause of 21 days) were administered intravenously and repeated every 3 to 4 weeks for a maximum of 4 to 6 cycles at the attending physicians' discretion (i.e. after 4 cycles, the physician decided whether a fifth and/or sixth cycle was appropriate). Treatment was continued until disease progression, unacceptable adverse events, or the patient's request for cessation.

Response evaluations

Lesions were evaluated using plain chest radiography, CT of the chest and abdomen, PET or bone scintigraphy, and CT or MRI of the cranium. PET or bone scintigraphy, as well as CT or MRI of the cranium, were performed at six-month intervals or earlier if patients had significant tumor-associated symptoms. Tumor control was assessed according to the Response Evaluation Criteria in Solid Tumors guidelines (version 1.1). The best overall response to first-line chemotherapy was recorded as the tumor response.

Statistical analyses

The PFS was defined as the interval between the date of starting first-line chemotherapy and that of disease progression or the patient's death. The OS was defined as the interval between the date of starting first-line chemotherapy and that of the patient's death or last follow-up. The PPS was recorded as the time from tumor progression until death or was otherwise censored on the date of the last follow-up. Survival curves were plotted using the Kaplan-Meier method. Spearman's rank correlation and linear regression analyses were used to determine whether the PFS or PPS was correlated with the OS. To identify factors that are predictive of the PPS, the proportional hazards model with a step-

wise regression procedure was applied. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using this model. PPS values were compared using the log-rank test. *P*-values less than 0.05 were considered significant. Statistical analyses were performed using the SPSS software program, version 23.0 for Windows (IBM Corp., Armonk, NY, USA).

Table 1. Patients' Characteristics (n = 75)

Gender	
Male/female	64/11
Age (years)	
Median (range)	72 (47-91)
Smoking history	
Current/former	75/0
ECOG performance status score	
0-1/2-3	47/28
Elderly, 0-1/2-3	47/12
Non-elderly, 2-3	16
Stage	
Limited-disease/extensive-disease	3/72
Brain metastasis	
Positive/negative	10/65
Type of relapse	
Sensitive/refractory	57/18
First-line chemotherapy	
CBDCA-based regimen/amrubicin	36/39
Response to first-line chemotherapy	
PR	51
SD/PD	15/9
Number of regimens after progression following first-line chemotherapy	
0/1/2/3	25/50/22/1
Median (range)	1 (0-3)

ECOG, Eastern Cooperative Oncology Group; CBDCA, carboplatin; PR, partial response; SD, stable disease; PD, progressive disease.

RESULTS

Patients' characteristics

Seventy-five patients who were treated between March 2010 and December 2017 were identified in this retrospective cohort study, all of whom were included in our analyses. The patients' demographic data are shown in Table 1. There were 64 men and 11 women with a median age of 72 years old. Forty-seven patients had good PS scores upon commencing first-line chemotherapy. The regimens of prior chemotherapy were as follows: 33 patients received CBDCA/ETP, 3 received CBDCA/irinotecan, and 39 received AMR monotherapy. After progression following first-line chemotherapy, only 50 of the 75 patients received subsequent chemotherapy. The median number of follow-up therapeutic regimens among all 75 patients was 1 (range 0-3 regimens). Fifty-one patients had either a partial response (PR) or stable disease (SD) following first-line chemotherapy, whereas 24 patients had progressive disease (PD).

The survival

With a median follow-up time of 10.5 months, the median PFS and OS for all patients were 6.1 (95% CI: 4.1-5.1) months (Figure 1a) and 11.8 (95% CI: 8.3-15.3) months (Figure 1b), respectively. The relationships between the

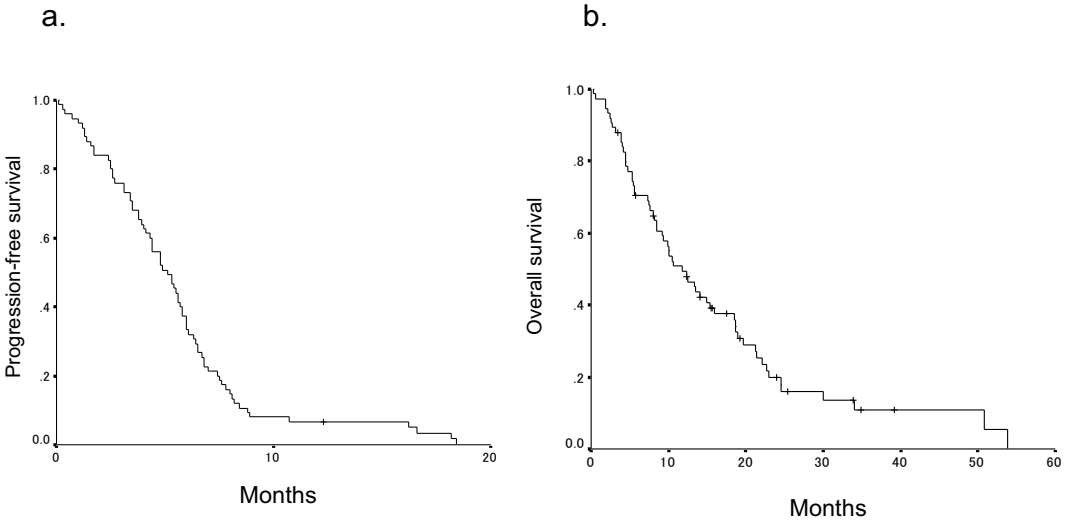

Figure 1. Kaplan-Meier plots showing the **(a)** progression-free survival and **(b)** overall survival of all patients.

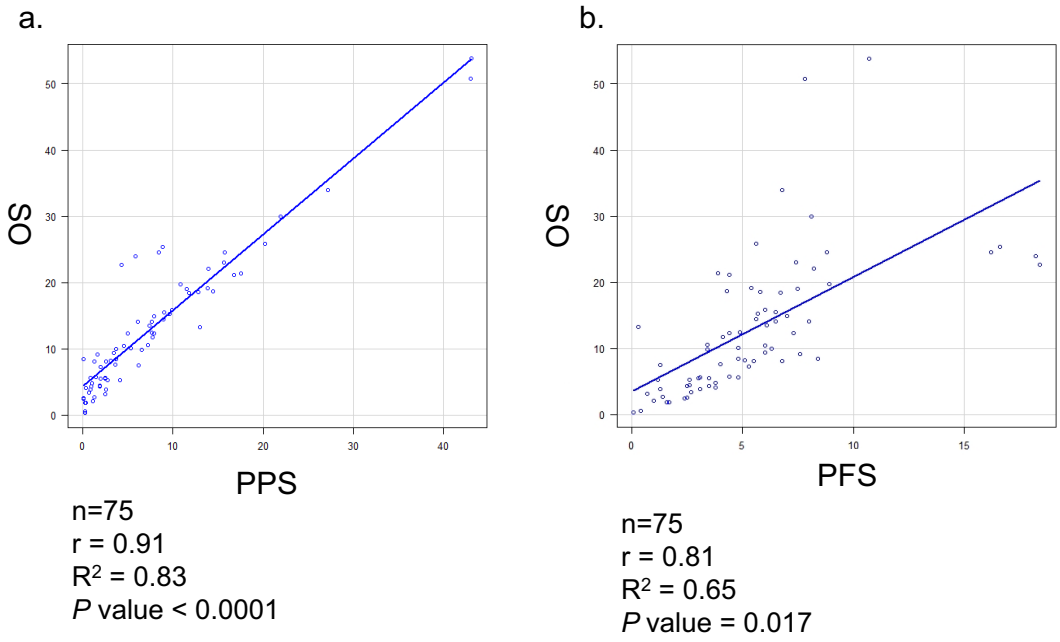

Figure 2. The analysis of the relationship between the **(a)** overall survival (OS) and post-progression survival (PPS), and the **(b)** OS and progression-free survival (PFS). There were 2 outliers in these data. *The r values represent Spearman's rank correlation coefficient. †The R^2 values represent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

OS and the PFS and PPS are shown in Figure 2. Based on Spearman's rank correlation coefficient and linear regression, the PPS was more strongly associated with the OS (r = 0.91, R^2 = 0.83, $P < 0.0001$; Figure 2a) than with the PFS (r = 0.81, R^2 = 0.65, P = 0.017; Figure 2b). In addition, the PPS was strongly associated with the OS regardless of the type of first-line regimen: CBDCA-based regimen (n = 36, r = 0.90, R^2 = 0.81, P = 0.001) vs. AMR monotherapy (n = 39, r = 0.91, R^2 = 0.83, P = 0.001). Regarding the 50 patients receiving second-line chemotherapy, the PPS was more strongly associated with the OS (r = 0.89, R^2 = 0.79, $P < 0.001$) than with the PFS (r = 0.78, R^2 = 0.61, P = 0.001). The relationship between the PFS and PPS was relatively weak (r = 0.55, R^2 = 0.325) compared to that between the OS and PPS.

The PPS was 3.7 (95% CI: 0.5-6.9) months in elderly patients with a poor PS (n=12). The PPS values were 4.3 months (95% CI: 1.2-7.4) and 6.5 months (95% CI: 0.2-12.8) in the non-elderly patients with a poor PS and the elderly patients with a good PS, respectively.

Among patients receiving a CBDCA-based regimen, 24 received AMR as a second-line therapy, achieving a median OS of 18.6 (95% CI: 14.1-23.1) months, and among patients receiving a AMR monotherapy, 26 received second-line chemotherapy achieving a median OS of 14.9 (95% CI: 11.8-19.0) months, respectively. Meanwhile, the median OS was 4.1 (95% CI: 2.1-6.1) months among 12 patients who did not receive second-line therapy after CBDCA-based chemotherapy failure.

Factors affecting the PPS

After observing a significant relationship between the PPS and OS, associations between the PPS and various clinical factors were assessed. In a univariate analysis, the response to first-line chemotherapy, the type of relapse (refractory/sensitive) to first-line chemotherapy, and whether or not second-line chemotherapy was administered were found to be significantly associated with the PPS (Table 2). A multivariate analysis revealed that the PS, type of relapse to first-line chemotherapy, first-line chemotherapy regimen (CBDCA-based vs. AMR monotherapy), and whether or not second-line chemotherapy was administered were significantly independent predictors of the PPS (Table 2). The PPS was 8.4 months (95% CI, 5.5-11.3) in patients receiving second-line chemotherapy, 7.6 months (95% CI, 3.5-11.7) in those with good PS scores at the time of first-line chemotherapy, 8.4 months (95% CI, 5.7-11.1) in those with sensitive relapse, and 8.4 months (95% CI, 3.3-13.5) in

Table 2. Univariate and Multivariate Analyses of Factors Potentially Associated with the Post-progression Survival

Variable	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
Gender Male vs. female	1.29 (0.63-2.63)	0.49		
Age (years) ＜75 vs. ≥75	0.92 (0.54-1.57)	0.76		
ECOG performance status score 0-1 vs. 2	1.58 (0.93-2.68)	0.089	1.79 (1.03-3.10)	0.039
Brain metastasis Positive vs. negative	0.81 (0.37-1.81)	0.61		
Response to first-line chemotherapy PR/CR vs. SD/PD	0.35 (0.20-0.60)	＜0.001	Excluded	
Type of relapse to first-line chemotherapy Sensitive vs. refractory	0.21 (0.11-0.39)	＜0.001	0.18 (0.09-0.36)	＜0.001
First-line chemotherapy regimen CBDCA-based vs. amrubicin	1.52 (0.91-2.57)	0.11	1.76 (1.03-3.03)	0.03
Second-line chemotherapy Positive vs. negative	0.26 (0.14-0.46)	＜0.001	0.25 (0.13-0.47)	＜0.001

CI, confidence interval.

those receiving a CBDCA-based regimen as a first-line therapy. Meanwhile, in patients who did not receive second-line chemotherapy, the PPS was only 1.3 months (95% CI, 0.3-2.3).

DISCUSSION

We evaluated the relationships between the OS and the PFS and PPS in elderly or poorly performing patients with ED-SCLC and found that the PPS after first-line chemotherapy was strongly associated with the OS, whereas only a moderate association with the PFS was noted. A recent clinical trial found the PPS to be strongly associated with the OS after first-line chemotherapy for advanced NSCLC, as did other studies of patients with advanced NSCLC and ED-SCLC.[11-15,18] While a previous study reported a significant association between the PPS and OS among good PS and non-elderly SCLC patients, the relationship between the OS and PPS, as well as predictors of the PPS in elderly or poor PS patients with ED-SCLC, have not been thoroughly explored. To our knowledge, ours is the first study to not only reveal the strong influence of the PPS on the OS but also to identify key predictors of the PPS in elderly or poorly performing patients with ED-SCLC.

A previous meta-analysis found that the PFS was a surrogate endpoint for the OS in patients with NSCLC, suggesting that the PFS may also be a surrogate endpoint for the OS in patients with ED-SCLC.[19,20] While the PFS did show a significant correlation with the OS in our study, it turned out that the PPS was much more strongly correlated with the OS than the PFS in elderly or poor-PS patients with ED-SCLC. It is equally important to emphasize that a (1) good PS, (2) sensitive relapse to first-line chemotherapy, (3) first-line chemotherapy by CBDCA-based regimen, and (4) performing second-line chemotherapy prolonged the PPS after progression following first-line chemotherapy, which is associated with a longer OS. In general, the PS and relapse pattern to first-line chemotherapy are associated with the OS and consequently with the PPS in non-elderly or good PS SCLC patients. Our findings were accordance with the above previous results.

The present study further suggested that 'performing second-line chemotherapy' is essential to achieve a favorable PPS in elderly or poor PS patients as well as non-elderly or good PS patients. In our institute, AMR was often administrated to such patients. We previously reported that CBDCA-based regimens remain a better first-line treatment for ED-SCLC in elderly patients or those with a poor PS than AMR.[21] Thus, 'first-line chemotherapy with a CBDCA-based regimen' was an independent predictor of the PPS in the present study.

Given these findings, we feel it is reasonable to recommended that elderly SCLC patients be provided second-line chemotherapy whenever possible if the above conditions (1) to (4) are satisfied.

Several clinical trials found that AMR significantly improved the response and survival rates in patients with relapsed SCLC.[22-25] Thus, AMR monotherapy has become the standard second-line chemotherapy for ED-SCLC in Japan. Furthermore, we previously reported that AMR monotherapy is feasible and effective for elderly patients with relapsed SCLC.[26] In the present study, patients receiving a CBDCA-based regimen as a first-line treatment followed by AMR as a second-line treatment achieved a median OS of 18.6 months, indicating that continuing chemotherapy using effective anticancer drugs can lead to a long-term survival in patients with SCLC. In contrast, an OS of 4.1 months was observed in patients who did not receive second-line therapy after CBDCA-based chemotherapy failure. It can be inferred from these results that AMR monotherapy is essential to achieving a long-term PPS in relapsed elderly or poor-PS patients with ED-SCLC. Imai et al. reported that the PPS has a greater influence on the OS in elderly patients with ED-SCLC after first-line chemotherapy[27]; their findings are consistent with ours.

Several limitations associated with the present study warrant mention. First, the results cannot be considered definitive owing to the study's retrospective, single-center design and relatively small sample size. Second, although the individuals included in this study were elderly or had a poor PS, their quality of life data were not evaluated. Third, because different physicians documented patient responses, the timing of the PFS evaluation and tumor response rates may have been less precise than would have been the case if only a single physician had documented all responses.

In conclusion, PPS has a greater influence on the OS than on the PFS in elderly or poor-PS ED-SCLC patients after first-line chemotherapy. These findings suggest that continuing treatment subsequent to first-line chemotherapy in such patients is beneficial in terms of achieving a long-term OS. The development of new anticancer drugs that are effective against SCLC is therefore warranted to improve the PPS as well as the OS. However, as our conclusions are based on a retrospective analysis, our findings ought to be validated in prospective studies.

本論文内容に関連する著者の利益相反：なし

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