Primary malignant melanoma of the trachea: A case report

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Abstract. Primary cancer of the trachea is rare and accounts for only 0.1-0.4% of all newly diagnosed respiratory tract cancers, worldwide. In the present study, a case of primary tracheal malignant melanoma, a particularly rare type of cancer, is reported. A 68-year-old male presented with a cough and bloody sputum. A chest computed tomography scan revealed a 25x20x15-mm tracheal tumor, located immediately above the carina, which reduced the cross-sectional area of the trachea by ~90%. Histopathological analysis of biopsy specimens determined a diagnosis of malignant melanoma. The patient was treated with argon plasma coagulation and chemoradiotherapy, which restored airway patency, however, metastasis was detected in the lungs. The patient refused further treatment and received palliative care. Subsequently, the patient succumbed to the disease within four months. Thus, although primary malignant melanoma of the trachea is extremeley rare, the possibility should be considered during diagnosis.

Introduction

Primary cancer of the trachea is particularly rare (1) and accounts for only 0.1-0.4% of all newly diagnosed respiratory tract cancers, which corresponds to 2.6 new cases per 1,000,000 individuals, annually, worldwide (2,3). Approximately 75% of these tumors are squamous cell carcinoma or adenoid cystic carcinoma (4). Malignant melanomas occur primarily as skin lesions and account for 2% of all skin tumors, worldwide (5). Although primary malignant melanoma frequently metastasize to the liver, lung, brain, or bone, this type of cancer rarely occurs in parts of the body other than the skin. The most uncommon form of extracutaneous melanoma is primary tracheal melanoma (6-10). In the present study, the case of a patient presenting with malignant melanoma of the trachea is reported to improve the current understanding of this rare disease. Written informed consent was obtained from the patient.

Case report

In March 2013, a 68-year-old male presented to the Department of Respiratory Medicine, Shizuoka City Hospital (Shizuoka, Japan) with a cough and bloody sputum, which had worsened over the previous two month and become intractable, with the development of stridor. A chest computed tomography (CT) scan revealed a 25x20x15-mm intratracheal lesion located immediately above the carina (Fig. 1), which reduced the cross-sectional area of the trachea by ~90%. Flexible bronchoscopy demonstrated these results and revealed an obstructive tumor surrounding the carina, as well as irregularly shaped, darkened regions in the tracheal mucosa (Fig. 2A).

Following biopsy of the tumor and the surrounding mucosa, the tumor was cauterized with argon plasma coagulation (APC) to restore airway patency, however, the presence of a residual tumor mass was not clear. Following cauterization, the patient experienced immediate symptomatic relief. The biopsy specimens were composed of tumor fragments and aggregated melanophages. Histologically, hematoxylin and eosin staining of the tumor demonstrated proliferation of epithelioid-shaped atypical cells with marginal melanin production (Fig. 3A). In addition, the tumor cells showed positive immunostaining for three melanoma markers, S-100, melan-A and HMB-45 (Fig. 3B-D). Subsequently, the tumor was diagnosed as a malignant melanoma. The biopsy specimens from the bronchial mucosa revealed a band-like accumulation of melanophages and lymphocytes beneath the tracheal epithelium. However, melanoma infiltration was not observed among the melanophages.

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Key words: malignant melanoma, trachea, argon plasma coagulation

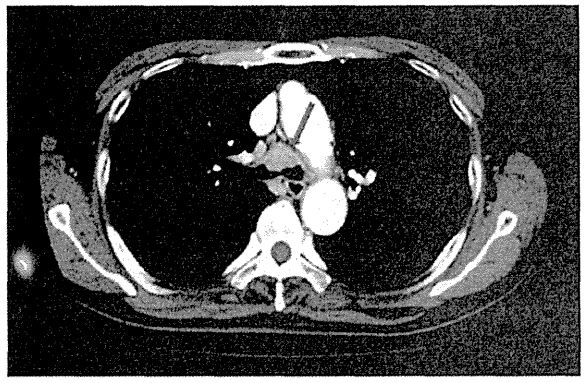

Figure 1. Chest computed tomography scan. The tumor measured 25x20x15 mm and was located directly above the carina and protruded from the anterior wall of the trachea (arrow).

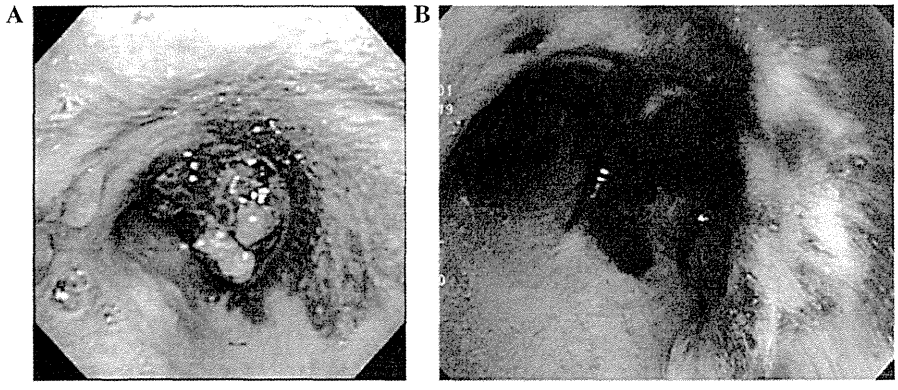

Figure 2. Endoscopic findings. (A) Prior to treatment, bronchoscopy revealed a pigmented, cauliflower-like, warty tumor. (B) Following chemoradiotherapy, bronchoscopy revealed darkened regions in the tracheal mucosa.

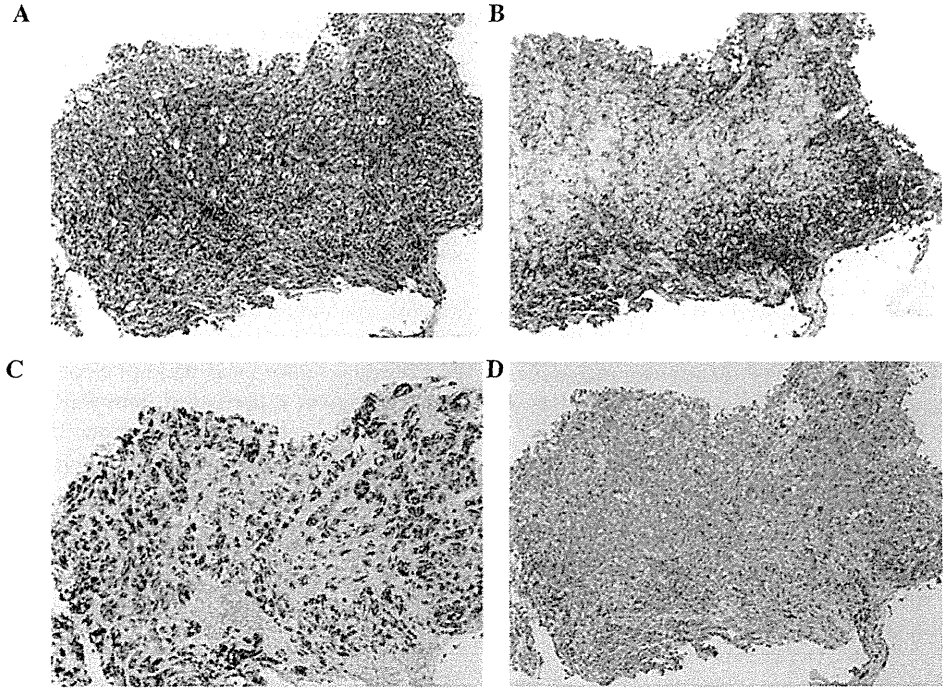

Figure 3. Histological and immunohistochemical observations of tumor tissue obtained via bronchoscopic biopsy. (A) Proliferation of epithelioid-shaped atypical cells with marginal melanin production were observed (stain, hematoxylin and eosin; magnification, x100). In the same tumor, these epithelioid-shaped atypical cells also stained positively for the melanoma markers (B) S-100, (C) melan-A and (D) HMB-45 (magnification, x100).

The patient did not have a history of previous surgeries or skin biopsies and did not exhibit melanoma-like skin lesions. In addition, magnetic resonance imaging and positron emission tomography did not reveal any metastatic lesions in the brain. The level of 5-S-cysteinyldopa, a biochemical marker of melanoma, which was 7.6 nmol/l (normal range, 1.5-8.0 nmol/l) at diagnosis, did not increase. As a result of these findings, it was hypothesized that the trachea was the primary site of the tumor and no metastasis had occurred at the time of clinical presentation.

The lesion was inoperable due to its large size; therefore, the patient was treated with a combination of dacarbazine-based chemotherapy (200 mg/m^2 dacarbazine, days 1-5) for three cycles every 4 weeks, for three months and thoracic radiotherapy (total dose, 65 Gy in 30 fractions). Following chemoradiotherapy, bronchoscopy revealed darkened regions of the tracheal mucosa (Fig. 2B). Subsequently, metastatic lesions appeared in the lungs and the 5-S-cysteinyldopa levels gradually increased, thus, chemotherapy was resumed.

Discussion

Primary tracheal malignant melanoma is particularly rare (6-10) and there are only a small number of reports regarding intratracheal metastasis (11). Various studies have investigated the oncogenesis of mucosal melanomas and have attempted to elucidate the histogenesis of lower respiratory tract melanomas (12,13). Theories include melanocytic migration during embryogenesis, transformation of respiratory epithelial cells into melanocytes and differentiation of neuroendocrine cells to melanocyte (12).

Pathological examination cannot distinguish primary melanoma from metastatic melanoma. The criteria for primary respiratory malignant melanoma diagnosis are as follows: A solitary lesion; 'dropping off' of melanoma cells together with junctional changes in the mucosa; invasion from the epithelium toward the submucosa; histologically identified presence of melanin; no prior skin lesions; and no familial history of cutaneous disease (12). In the present case, no other primary lesions were identified on radiological or dermatological examination. The patient was diagnosed with a primary tracheal malignant melanoma on the basis of three criteria: The lack of a history of skin lesions and a family history of cancer; the presence of a solitary tumor surrounded by abnormal mucosa; and positive immunostaining for three melanoma markers, S-100, melan-A and HMB-45. These results are consistent with the diagnostic criteria for primary malignant melanoma in the respiratory tract (13,14).

Tracheal tumors may be fatal as they occasionally obstruct the airway. However, due to their rarity, no standard treatment has been identified. Treatment is either palliative, which aims to restore airway patency, or therapeutic, with tracheal resection and end-to-end anastomosis (15). In the current case, APC was conducted to restore airway patency. This indicated that treating tracheal tumors with APC may be an effective type of palliative therapy to provide immediate relief, as well as long-term improvements in patient quality of life. Although it is useful to combine palliative measures with therapeutic agents, including radiation and biological or chemical agents, the current treatment strategies are inadequate. For example, radiotherapy may be an effective method to locally control tracheal melanoma, however, it does not improve long-term survival (16).

In conclusion, the patient in the current case was treated with radiation and dacarbazine-based chemotherapy, which is a standard chemotherapeutic agent for malignant melanoma. Initially, the radiotherapy facilitated with controlling the local spread of the tumor, however, follow-up CT scans revealed distant metastasis to the lungs. In future, targeted cancer therapies using molecules, such as BRAF inhibitors, and cytotoxic T-lymphocyte-associated protein, programmed cell death protein 1 and programmed death-ligand 1 antibodies (17-20), may be effective options for treating cases of advanced malignant melanoma, including those originating in the trachea.

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Original Article

Progression-free survival, post-progression survival, and tumor response as surrogate markers for overall survival in patients with extensive small cell lung cancer

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Abstract:

OBJECTIVES: The effects of first-line chemotherapy on overall survival (OS) might be confounded by subsequent therapies in patients with small cell lung cancer (SCLC). We examined whether progression-free survival (PFS), post-progression survival (PPS), and tumor response could be valid surrogate endpoints for OS after first-line chemotherapies for patients with extensive SCLC using individual-level data.

METHODS: Between September 2002 and November 2012, we analyzed 49 cases of patients with extensive SCLC who were treated with cisplatin and irinotecan as first-line chemotherapy. The relationships of PFS, PPS, and tumor response with OS were analyzed at the individual level.

RESULTS: Spearman rank correlation analysis and linear regression analysis showed that PPS was strongly correlated with OS ($r = 0.97$, $p < 0.05$, $R^2 = 0.94$), PFS was moderately correlated with OS ($r = 0.58$, $p < 0.05$, $R^2 = 0.24$), and tumor shrinkage was weakly correlated with OS ($r = 0.37$, $p < 0.05$, $R^2 = 0.13$). The best response to second-line treatment, and the number of regimens employed after progression beyond first-line chemotherapy were both significantly associated with PPS ($p \leq 0.05$).

CONCLUSION: PPS is a potential surrogate for OS in patients with extensive SCLC. Our findings also suggest that subsequent treatment after disease progression following first-line chemotherapy may greatly influence OS.

Key words:

Extensive small cell lung cancer, overall survival, post-progression survival, progression-free survival, tumor response

Lung cancer is one of the leading causes of cancer-related mortality worldwide. In 2007, 1.3 million people were diagnosed with lung cancer, 15-20% of whom were found to have small cell lung cancer (SCLC).[1,2] Overall survival (OS) is considered the most reliable endpoint in cancer studies, and when studies can be conducted to adequately assess survival, it is usually the preferred endpoint.[3] OS is a precise endpoint, is easy to measure, and can be documented by the date of death. Surrogate endpoints such as tumor response and progression-free survival (PFS) are also useful endpoints for phase II oncology clinical trials because they can be measured earlier and more conveniently. Events for these surrogate endpoints occur more frequently than do events for the main endpoints of interest, which are referred to as the true endpoints.

The effects of first-line chemotherapy on OS might be confounded by subsequent therapies. Indeed, PFS improvements do not necessarily result in an improved OS, as shown by recent randomized trials in patients with non-SCLC (NSCLC).[4] In recent years, a growing number of active compounds have become available as second- or third-line chemotherapy for breast, ovarian, and colorectal cancers[5-7], as well as advanced NSCLC. However, with respect to the treatment of SCLC, first-line chemotherapy is often beneficial for patients with poor performance status (PS), in contrast with NSCLC cases, albeit at the risk of serious toxic effects. SCLC is a distinct clinical and histological entity within the range of lung cancers. Only a few drugs are available for its treatment, and topotecan is currently the only drug approved for the treatment of relapsed SCLC patients in the United States.[8-10] Second-line treatment is an option in only a few patients, owing to rapid disease progression and poor PS.

Although PFS following first-line chemotherapy has not been validated as a surrogate endpoint for OS, post-progression survival (PPS) has been shown to be strongly associated with OS after first-line chemotherapy for advanced NSCLC.[11,12] Furthermore, it has been suggested that OS can be approximated as the sum of PPS and PFS.[3] Very few novel anticancer drugs have become available for extensive SCLC, and the relationship between PPS and OS in extensive SCLC remains unclear.

At the level of the individual patient, it is of interest to assess the effect of therapy administered after disease progression on survival. The validation of surrogate measures for OS after first-line therapy in individual patients with advanced NSCLC has been reported previously.[13] Further, the surrogate endpoint sometimes does not reflect the primary endpoint. The significance of PPS in SCLC also remains unclear at the level of the individual patient. Therefore, it is important to establish whether PFS, PPS, or tumor response could be valid surrogate endpoints for OS after first-line therapy in patients with extensive SCLC using individual-level data.

The first-line treatment of choice in extensive-stage SCLC remains 4 to 6 cycles of platinum combination chemotherapy.[1] Although many patients initially achieve clinical remission or disease control with first-line chemotherapy, most subsequently experience disease progression and eventually die of extensive SCLC. We examined first-line cisplatin and irinotecan combination chemotherapy because it is considered the standard first-line chemotherapy in these cases.[1] Previously, in a phase 3 study of extensive SCLC, first-line chemotherapy with irinotecan plus cisplatin was found to be more effective than etoposide/cisplatin (median survival of 12.8 months versus 9.4 months, $p = 0.002$).[14] The MST of patients with extensive SCLC was approximately 1 year. For extensive SCLC patients, OS is shorter and options for subsequent chemotherapy are limited.

In the present study, we analyzed the relationships of PFS, PPS, and tumor response with OS in patients with extensive SCLC at the individual level. The patients recruited to this study had only a limited number of options for subsequent-line chemotherapy. We also explored the prognostic value of baseline and tumor characteristics for PPS.

Methods

Patients

Between September 2002 and November 2012, 60 patients with extensive SCLC were treated with cisplatin and irinotecan as first-line chemotherapy and were enrolled in this study. The tumor response was not evaluated in 10 cases, and PFS data were censored in one case. These 11 patients were excluded from the analyses to maintain uniformity in patient background characteristics. Thus, data from 49 patients were analyzed. The study protocol was approved by the Institutional Review Board of Shizuoka Cancer Center (#.25-J91-25-1-3).

The patients in this study were treated with cisplatin (60 $mg \cdot m^{-2}$ day^{-1} for 1 day, followed by a pause of 28 days) and irinotecan (60 $mg \cdot m^{-2} day^{-1}$ on days 1, 8, and 15, followed by a pause of 28 days). This cycle was repeated every 28 days for a maximum of six courses.

The best overall response and maximum tumor shrinkage were recorded as tumor responses. Radiographic tumor responses were evaluated according to the Response Evaluation Criteria In Solid Tumors,ver. 1.1[15]: 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. 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 consultation. PPS was recorded as the time from tumor progression until death or was censored on the date of the last follow-up consultation. In this study, we defined treatment-free interval (TFI) as the period from the date of completion of first-line treatment to the first relapse. When prophylactic cranial irradiation (PCI) was performed as first-line treatment, the date of completion was defined as the last day of these treatments. We defined sensitive relapse as TFI $\geq$ 90 days, based on the definition in several previous trials.[16,17]

Statistical analyses

To examine whether PFS, PPS, or tumor shrinkage was correlated with OS, we used Spearman rank correlation analysis and linear regression analysis. 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 the 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 9.0 for Windows (SAS Institute, Cary, NC, USA).

Results

Patient characteristics and treatment efficacy

Of the 49 patients included in the analyses, 43 patients died; the median follow-up time was 14.0 months (range, 0.7-36.8 months). The characteristics of the 49 patients (median age, 63 years; range, 43-75 years) included in the present study are shown in Table 1. Target lesions were not evaluated in one of the cases. One, 38, 5, and 4 patients showed CR, PR, SD, and PD, respectively. The response rate was 79.6% and the disease control rate was 91.8%.

After progressing past first-line chemotherapy, 5 of the 49 patients did not receive further chemotherapy. The other 44 patients received subsequent chemotherapy after completing their first-line chemotherapy. Among the 49 patients, the median number of follow-up therapeutic regimens was 2 (range, 0-5 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 paclitaxel was the most common third-line chemotherapy agent.

The median PFS and OS were 5.5 months and 13.9 months, respectively [Figure 1a, 1b].

Table 1: Baseline patient characteristics

Characteristic	
Gender	
Male/female	44/5
Median age at treatment (years)	63 (43-75)
Performance Status (PS)	
0/1/≥2	13/32/4
Histology	
Small cell carcinoma/others	49/0
Stage	
IIIB/IV	0/49
Number of first-line chemotherapy courses	
1/2/3/4/5/6	1/4/3/38/2/1
Median (range)	4 (1-6)
Number of regimens after progression following first-line chemotherapy	
0/1/2/3/4/5	5/18/13/8/3/2
Median (range)	2 (0-5)
Median sum of target lesion diameters [mm] (range)	112 (29-287)
Prophylactic cranial irradiation	
Yes/No	3/46
Median treatment-free interval [days] (range)	68 (29-287)

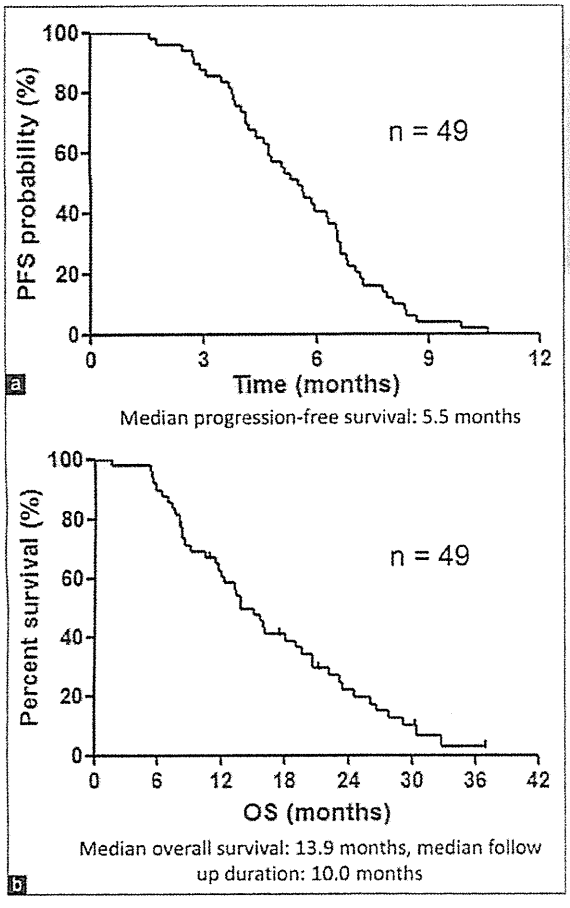

Figure 1: (a) Kaplan-Meier plots showing progression-free survival (PFS) (b) Kaplan-Meier plots showing overall survival (OS)

Relationship between OS and PFS, PPS, and tumor shrinkage

The relationship between OS and PFS, PPS, and tumor shrinkage is shown in Figure 2a, 2b, and 2c, respectively. PPS

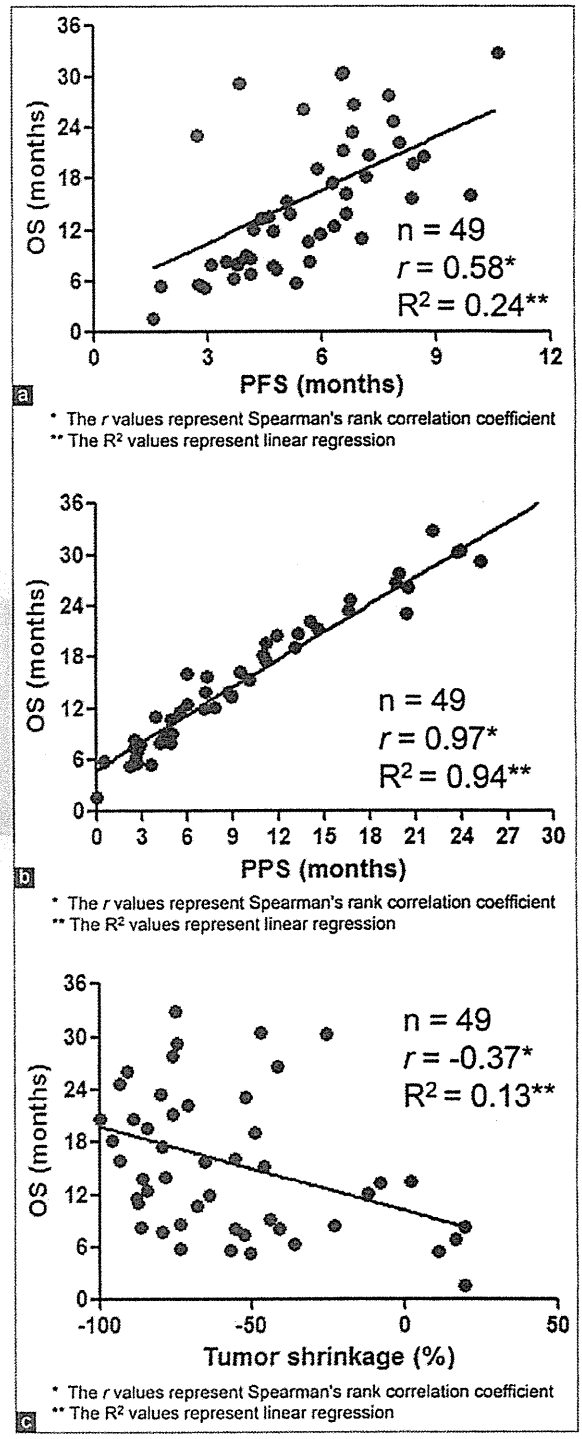

Figure 2: (a) Correlation between overall survival (OS) and progression-free survival (PFS) (b) Correlation between overall survival (OS) and post-progression survival (PPS) (c) Correlation between overall survival (OS) and tumor shrinkage

was strongly associated with OS ($r = 0.97$, $p < 0.05$, $R^2 = 0.94$), based on Spearman's rank correlation coefficient and linear regression, whereas PFS was moderately correlated with OS ($r = 0.58$, $p < 0.05$, $R^2 = 0.24$). Furthermore, tumor shrinkage was only weakly correlated with OS ($r = 0.37$, $p < 0.05$, $R^2 = 0.13$).

Factors affecting post-progression survival

PPS was strongly associated with OS. Therefore, the association between PPS and various clinical factors was assessed. In the univariate analysis [Table 3], PS at the end of first-line treatment, at the beginning of second-line treatment, and TFI (≥90/<90 days) as well as the best response at first-line treatment, the best response from the second-line treatment, and the number of regimens employed after progression beyond first-line chemotherapy were found to be associated with PPS ($p < 0.05$). Next, a multivariate analysis for PPS was conducted [Table 4]. This revealed that the best response after second-line treatment (non-PD/PD), and the number of regimens employed after progression following first-line chemotherapy were significantly associated with PPS ($p \leq 0.05$). The log-rank tests confirmed that PPS was significantly associated with the best response at second-line treatment (non-PD/PD), and the number of regimens employed ($p < 0.05$; Figure 3a and 3b). Based on the best response at second-line treatment, patients with non-PD had a median PPS of 13.1 months, which was longer than that of their counterparts, who had a median PD of 7.2 months (log-rank, $p = 0.05$; Figure 3a). According to the number of regimens employed after progression following first-line chemotherapy, the median PPS for those who were not administered additional regimens was 3.5 months; with 1 additional regimen, the median PPS was 5.5 months; and with ≥2 regimens, the median PPS was 14.1 months, (log-rank test, $p < 0.01$; Figure 3b). These results remained consistent after adjustment using the Cox proportional hazards models [Table 4].

Discussion

We examined the relationships of OS with PFS, PPS, and tumor shrinkage at the individual level in patients with extensive small cell lung cancer.PPS was strongly associated with OS, whereas PFS and tumor shrinkage were moderately and weakly correlated with OS, respectively. 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.

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

	Second-line	≥Third-line	Total
CDDP+irinotecan re-challenge	3	1	4
CDDP+VP16	2	1	3
CBDCA+VP16	2	4	6
CBDCA+PTX	0	3	3
Amrubicin	27	10	37
Topotecan	3	4	7
Paclitaxel	3	12	15
Irinotecan	0	2	2
Gemcitabine	3	7	10
Others	1	1	2

The validity of surrogate endpoints has been previously determined through meta-analyses.[18,19] In recent years,

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

Factors	Post-progression survival		
	Hazard ratio	95% CI	*p* value
Gender	1.06	0.42-3.56	0.907
Age (years) at the beginning of first-line treatment	0.97	0.93-1.02	0.341
PS at the beginning of first-line treatment	1.20	0.70-2.05	0.490
Number of courses of first-line treatment administered	0.67	0.46-1.02	0.066
Sum of target lesion diameters	1.00	0.99-1.00	0.102
Best response at first-line treatment			
PR/non-PR	0.65	0.31-1.53	0.306
Non-PD/PD	0.22	0.08-0.77	0.021
PS at the end of first-line treatment	4.45	2.22-9.36	<0.001
Prophylactic cranial irradiation	0.81	0.28-3.39	0.738
Treatment-free interval (≥90/<90 days)	2.07	1.10-4.86	0.023
Age at the beginning of second-line treatment	0.96	0.92-1.01	0.196
PS at the beginning of second-line treatment	2.04	1.26-3.32	0.003
Best response following second-line treatment			
PR/non-PR	0.82	0.34-1.73	0.627
Non-PD/PD	0.48	0.24-0.92	0.028
Number of regimens after progression beyond first-line chemotherapy	0.50	0.35-0.70	<0.001

95% CI = 95% Confidence interval, PS = Performance status, PR = Partial response, PD = Progressive disease

Table 4: Multivariate Cox regression analysis of performance status (PS) at the end of first-line treatment, PS at the beginning of second-line treatment, best response at first-line treatment, best response at second-line treatment, and number of regimens employed after progression beyond first-line chemotherapy for post-progression survival

Factors	Post-progression survival		
	Hazard ratio	95% CI	*p* value
PS at the end of first-line treatment	1.81	0.60-6.10	0.29
PS at the beginning of second-line treatment	1.00	0.44-2.10	0.99
Best response at first-line treatment			
Non-PD/PD	0.50	0.14-2.34	0.34
Best response at second-line treatment			
Non-PD/PD	0.49	0.23-1.00	0.05
Number of regimens employed after progression beyond first-line chemotherapy	0.61	0.41-0.86	<0.01

95% CI = 95% Confidence interval, PD = Progressive disease

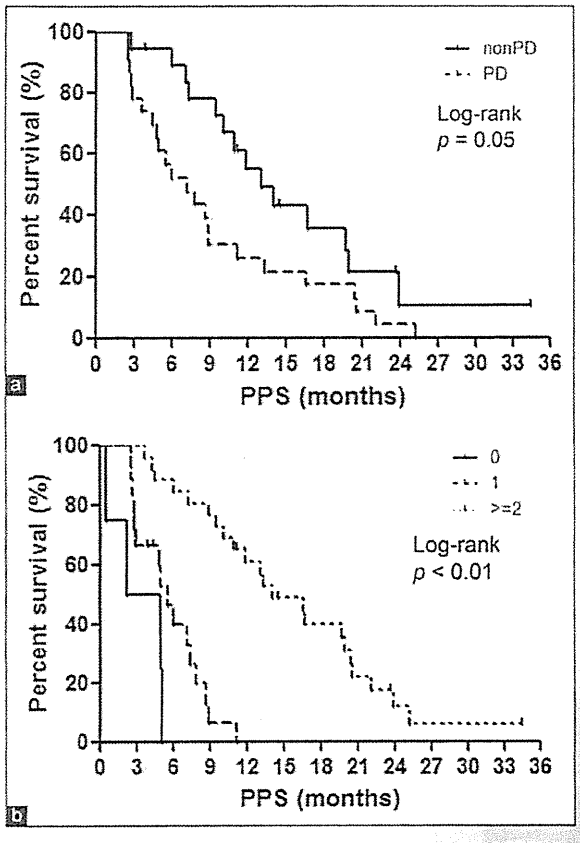

Figure 3: (a)Kaplan-Meier plots showing post-progression survival (PPS), according to the best response following second-line treatment Non-progressive disease (non-PD), median = 13.1 months; progressive disease (PD), median = 7.1 months. (b) Kaplan-Meier plots showing post-progression survival (PPS), according to the number of regimens after progression No further regimen, median = 3.5 months; 1 regimen, median = 5.5 months; 2 regimens, median = 14.1 months

biostatisticians have proposed a wide variety of measures for validating surrogate endpoints.[20,21] Although PFS is a potential surrogate endpoint for OS in extensive stage SCLC[22], its validity remains controversial. Broglio *et al.* recently focused on PPS, which they termed survival post progression (defined as OS minus PFS), in a hypothetical clinical trial setting under the assumption that treatment affected PFS but not PPS.[3] Recently, PPS was found to be strongly associated with OS after first-line chemotherapy for advanced NSCLC in a clinical trial[11,12], and we have previously reported the significance of PPS for advanced NSCLC based on an analysis of individual patients.[13]

In contrast with the findings of a previous study[22], we did not observe that PFS was a surrogate endpoint for OS in extensive stage SCLC, although PPS was not evaluated in the previous study. We analyzed our results pertaining to first-line therapy, which suggested that PFS and tumor response 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 with patients expected to have a short PFS after first-line chemotherapy, for example those with extensive 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 with a molecular targeted agent.[11] Studies based on individual advanced NSCLC patients revealed that a long PPS was associated with the PS at the beginning of second-line treatment, the best response after second-line treatment (non-PD/PD), and the number of regimens employed after disease progression following first-line chemotherapy.[13] To date, however, no predictive factors for PPS in cases of extensive SCLC have been identified. We studied the prognostic value of baseline factors for PPS in individual patients. We found that the best response after second-line treatment, and the number of regimens employed after progression following first-line chemotherapy were strongly associated with PPS. Moreover, we confirmed the significance of these relationships using log-rank tests. Our findings suggest that patients for 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 following first-line chemotherapy probably reflects the increasing number of available drugs, such as amrubicin, paclitaxel, and topotecan, which are available as second- or third-line chemotherapy for extensive 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 small. However, because relatively few extensive SCLC patients are treated with first-line cisplatin and irinotecan 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 will include a larger patient cohort, and more detailed examination is warranted. Second, we could not thoroughly evaluate treatments after progression following second-line chemotherapy, although only a few patients received third-line or subsequent chemotherapy. Third, the date on which a response was recorded was decided by each physician, which might have introduced variance in the PFS and tumor response rate. Fourth, chemotherapy regimens differ between Japan and the USA. In Japan, based on the results of a Japanese phase III trial[14], standard first-line chemotherapy for extensive SCLC currently is cisplatin combined with irinotecan. This combination is also described in the National Comprehensive Cancer Network guidelines as a suitable treatment option. Amrubicin is an effective second-line chemotherapy drug in a number of cancers including SCLC. In a phase III trial, it resulted in a significantly improved response rate compared to topotecan and also improved survival, especially in the subgroup of refractory patients.[23] On the basis of this trial,

amrubicin is now the standard second-line chemotherapy agent for extensive SCLC in Japan.

In conclusion, using individual patient data, PFS and tumor response were not found to be ideal surrogates for OS in patients with extensive SCLC who had limited options for subsequent chemotherapy. However, in these patients, PPS, rather than PFS, was strongly associated with OS. In addition, the best response after second-line treatment (non-PD/PD), and the number of regimens employed after disease progression following first-line chemotherapy were prognostic factors for PPS. Thus, the treatment course after progression following first-line chemotherapy greatly influences OS. We believe these findings justify further study to validate PPS as a surrogate marker of OS in patients with extensive SCLC.

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ORIGINAL ARTICLE

Effect of platinum-based chemotherapy for non-small cell lung cancer patients with interstitial lung disease

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Abstract
Purpose The prognosis of non-small cell lung cancer (NSCLC) patients with interstitial lung disease (ILD) is unclear. To assess the prognosis of NSCLC patients with ILD treated with platinum-based chemotherapy, we retrospectively analyzed the clinical course of those with ILD.
Methods One hundred and four NSCLC patients with ILD treated with platinum-based chemotherapy at Shizuoka Cancer Center between August 2002 and June 2013 were retrospectively reviewed.
Results The combination of carboplatin with paclitaxel was most frequently used as the first-line treatment for NSCLC patients with ILD (61 %). The overall response rate was 38 % in 104 NSCLC patients with ILD treated with platinum-based chemotherapy. In all patients, median progression-free survival and overall survival were 4.8 and 9.9 months, respectively. During first-line platinum-based chemotherapy, 9 % of the 104 patients with ILD developed chemotherapy-related exacerbation of ILD. Multivariate analysis demonstrated that clinical stage was a significantly independent prognostic factor (hazard ratio 0.517; 95 % confidence interval 0.314–0.842, $p = 0.0079$). Patients with clinical stage IV or recurrence after surgical resection showed poor prognosis (median survival time 8.5 months).
Conclusions Our study suggests that the prognosis of NSCLC patients with ILD is poor. The risk of exacerbation of ILD in patients treated with platinum-based chemotherapy as the first-line treatment was slightly lower than in previous reports.

Keywords Lung cancer · Non-small cell lung cancer · Interstitial lung disease · Platinum-based chemotherapy · Exacerbation

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Introduction

Lung cancer is the leading cause of cancer mortality; however, the prognosis of patients with non-small cell lung cancer (NSCLC) has been gradually improving. In lung adenocarcinoma, the development of targeted therapies for driver genes, including EGFR and ALK, has advanced [1–4]. On the other hand, preexisting interstitial lung disease (ILD) and idiopathic interstitial pneumonia are reported to be risk factors for drug-related ILD [5]. A large prospective cohort study of gefitinib, an epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), has shown that preexisting ILD is a strong risk factor for gefitinib-related ILD as well as cytotoxic chemotherapy-related ILD [6].

NSCLC patients with ILD have been excluded from most clinical trials. In the first-line chemotherapy for NSCLC patients, platinum-based chemotherapy is considered as the standard care [7, 8]. However, severe ILD has been reported in patients treated with cytotoxic chemotherapy agents, such as gemcitabine, docetaxel, and amrubicin [9–11]. Because NSCLC patients with ILD have few alternatives for cytotoxic chemotherapy drugs, the prognosis of

these patients remains unclear. In addition, our previous study showed the incidence of exacerbation of ILD was significantly higher in patients with lung cancer with usual interstitial pneumonia (UIP) pattern on CT findings than in those with non-UIP pattern [12].

This study aimed to assess the prognosis of NSCLC patients with ILD treated with platinum-based chemotherapy by retrospectively analyzing the clinical course of lung cancer patients with ILD.

Methods

The medical records of NSCLC patients with ILD treated with platinum-based chemotherapy were retrospectively reviewed at the Shizuoka Cancer Center between August 2002 and June 2013. Platinum-based chemotherapy was defined as doublet or triplet chemotherapy regimens that included cisplatin or carboplatin. Patients who received thoracic radiotherapy as a first-line treatment were excluded from this study. Pretreatment computed tomography (CT) scans of the chest were evaluated by a radiologist (ME) and two pulmonologists (HK and TN), who had no knowledge of the patient's outcome. ILD was diagnosed on the following criteria: ground-glass opacity, consolidation, or reticular shadow in both the lung fields. On the basis of CT characteristics, we divided patients with ILD into two groups: UIP pattern and non-UIP pattern, as described in our previous report [12].

Chemotherapy-related exacerbation of ILD was diagnosed on the basis of CT findings (bilateral ground-glass abnormality with or without focal consolidation, superimposed on the pretreatment interstitial shadow) [13]. Patients with an apparent pulmonary infection, pulmonary embolism, or heart failure were excluded. Chemotherapy-related exacerbation of ILD was evaluated based on pneumonitis using National Cancer Institute Common Terminology Criteria version 4.0. To assess the incidence of exacerbation of ILD by treatment regimen, the interval between the last administration of cytotoxic chemotherapy and the onset of exacerbation of ILD was defined as 4 weeks or less.

To identify prognostic factors for NSCLC patients with ILD treated with platinum-based chemotherapy, univariate and multivariate analyses were conducted. All categorical variables were analyzed using the Chi-square test or Fisher's exact test, as appropriate. Continuous variables were analyzed using the Mann–Whitney U test. Multivariate analyses were conducted using Cox proportional hazard models to assess the relationship between various factors and the prognosis of NSCLC patients with ILD. Responses were evaluated based on Response Evaluation Criteria in Solid Tumors version 1.1 criteria [14]. Overall survival (OS) was defined as the time from the start of platinum-based chemotherapy as a first-line treatment to death, and progression-free survival (PFS) was defined as the time from the start of platinum-based chemotherapy to disease progression or death. Event time was estimated using the Kaplan–Meier method. The log-rank test was used to compare cumulative survival in each group. All p values were reported as two sided, and values <0.05 were considered statistically significant. The study protocol was approved by the Institutional Review Board of Shizuoka Cancer Center (Nagaizumi-cho Sunto-gun, Japan).

Results

Patient characteristics

One hundred and four patients were diagnosed with NSCLC and ILD and treated with platinum-based chemotherapy as the first-line treatment. The characteristics of the patients receiving platinum-based chemotherapy are shown in Table 1. The median patient age was 67 (range 44–78) years, and almost all patients were male smokers with good performance status. Histologically, adenocarcinoma and squamous cell carcinoma were observed in 50 (48 %) and 47 (45 %) patients, respectively. Other diagnoses included large cell carcinoma and non-small cell carcinoma. Stages III and IV were observed in 39 and 53 % of the patients, respectively, and recurrence after surgical resection was observed in 7 %. Based on pretreatment CT of the chest, UIP and non-UIP patterns were observed in 70 (67 %) and 34 (33 %) patients, respectively. There were no significant differences in patient characteristics between the two groups.

Efficacy of platinum-based chemotherapy

The platinum-based chemotherapy regimens frequency as the first-line treatment is shown in Table 2. The combination of carboplatin with paclitaxel was most frequently used as the first-line treatment for NSCLC patients with ILD. Eighty-five (82 %) patients received chemotherapy regimens including carboplatin and 19 (18 %) received regimens including cisplatin. The overall response rate of 104 NSCLC patients with ILD treated with platinum-based chemotherapy was 38 % (Table 3). In all patients, the median PFS and OS were 4.8 and 9.9 months, respectively (Fig. 1). In patients treated with a combination of carboplatin with paclitaxel as the first-line treatment, the response rate, median PFS, and median OS were 35 %, 4.4, and 8.2 months, respectively.

Incidence of platinum-based chemotherapy-related exacerbation of ILD

Of the 104 patients with ILD, 26 (25 %) developed cytotoxic chemotherapy-related exacerbation. During first-line

Table 1 Patient characteristics (overall, $N = 104$)

	Total	UIP pattern	(%)	Non-UIP pattern	(%)	*p* value
No. of patients	104	70		34		
Gender						
Male	95	66	(94)	29	(85)	0.139
Female	9	4	(6)	5	(15)	
Age (year)						
Median	67	68		65		0.149
(range)	(44–78)	(53–78)		(44–75)		
Smoking status						
Current smoker	51	34	(49)	17	(50)	0.891
Former smoker	53	36	(51)	17	(50)	
Never smoker	0	0	(0)	0	(0)	
Performance status (ECOG)						
0–1	96	67	(96)	29	(85)	0.072
2	8	3	(4)	5	(15)	
Histology						
Adenocarcinoma	50	29	(42)	21	(62)	0.125
Squamous cell carcinoma	47	36	(51)	11	(32)	
Others	7	5	(7)	2	(6)	
Clinical stage						
IIIA–IIIB	41	31	(44)	10	(29)	0.338
IV	55	34	(49)	21	(62)	
Recurrence after surgical resection	8	5	(7)	3	(9)	

Table 2 Frequency of platinum-based chemotherapy regimens as first-line treatment and incidence of chemotherapy-related exacerbation of ILD ($N = 104$)

	No. of patients administered	No. of patients with exacerbation of ILD (%)
Carboplatin + paclitaxel	63	5 (8)
Carboplatin + S1	7	0
Carboplatin + gemcitabine	6	1 (17)
Carboplatin + paclitaxel + bevacizumab	5	2 (40)
Carboplatin + other drugs	4	0
Cisplatin + vinorelbine	6	0
Cisplatin + docetaxel	4	1 (25)
Cisplatin + S−1	3	0
Cisplatin + etoposide	3	0
Cisplatin + other drugs	3	0

ILD interstitial lung disease

platinum-based chemotherapy, nine (9 %) patients developed chemotherapy-related exacerbation of ILD. Eight (89 %) of the nine patients developed grade 3 or worse pulmonary toxicities, and two (22 %) patients died due to treatment-related causes within 4 weeks after exacerbation of ILD. Of 63 patients treated with a combination of carboplatin with paclitaxel, five (8 %) developed cytotoxic chemotherapy-related exacerbation of ILD. The incidence rate of exacerbation of ILD by each chemotherapy regimen is shown in Table 2.

Subsequent chemotherapy after platinum-based chemotherapy for NSCLC patients with ILD

Of the 104 included patients, 57 (55 %) received subsequent chemotherapy after platinum-based chemotherapy. Docetaxel (42 %) and vinorelbine (12 %) were most frequently used for subsequent chemotherapy. Of those patients who received second-line or subsequent chemotherapy, 17 (30 %) developed chemotherapy-related exacerbation of ILD (Table 4).

Table 3 Response of platinum-based chemotherapy for NSCLC patients with ILD ($N = 104$)

	All patients ($N = 104$)		Carboplatin + paclitaxel ($N = 63$)	
	No. of patients	(%)	No. of patients	(%)
Complete response	0		0	
Partial response	40	(38)	22	(35)
CR + PR	40	(38)	22	(35)
95 % Confidence interval	29.6–48.1		24.3–47.3	
Stable disease	44	(42)	28	(44)
Progression disease	13	(13)	8	(13)
Not evaluable	7	(7)	5	(8)

NSCLC non-small cell lung cancer, *ILD* interstitial lung disease, *CR* complete response, and *PR* partial response

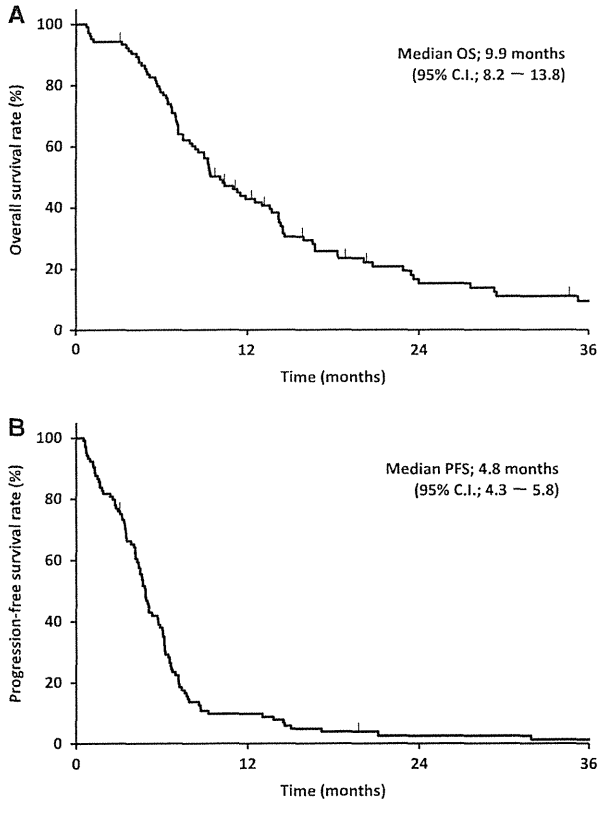

Fig. 1 **a** Overall survival curve including all 104 NSCLC patients with ILD. **b** Progression-free survival curve including all 104 NSCLC patients with ILD. *OS* overall survival, *PFS* progression-free survival, *NSCLC* non-small cell lung cancer, and *ILD* interstitial lung disease

Prognostic factors for NSCLC patients with ILD treated with platinum-based chemotherapy

The univariate and multivariate analyses results of survival for NSCLC patients with ILD treated with platinum-based chemotherapy are shown in Table 5. In univariate analysis, patients diagnosed with clinical stage III disease showed significantly better survival than those with clinical stage IV or recurrence after surgical resection (median survival time, 13.8 vs. 8.5 months, $p = 0.0237$, Fig. 2). Multivariate analysis also demonstrated that clinical stage was a significantly independent prognostic factor (hazard ratio 0.524; 95 % confidence interval 0.320–0.850).

Table 4 Frequency of chemotherapy regimens as second-line or subsequent treatment and incidence of chemotherapy-related exacerbation of ILD ($N = 57$)

	No. of patients administered	No. of patients with exacerbation of ILD (%)
Docetaxel	27	7 (26)
S1	16	3 (19)
Vinorelbine	10	2 (20)
Pemetrexed	8	2 (25)
Gefitinib	5	0
Carboplatin + paclitaxel	5	0
Nedaplatin	4	0
Other regimens	15	3 (20)

ILD interstitial lung disease

Discussion

In most clinical trials, NSCLC patients with ILD are excluded; therefore, little data on the prognosis of these patients are available. In this study, we evaluated the prognosis of NSCLC patients with ILD treated with platinum-based chemotherapy as the first-line treatment. A Japanese prospective study to evaluate the safety and efficacy of weekly paclitaxel in combination with carboplatin for advanced NSCLC with idiopathic interstitial pneumonia showed that median survival time was 10.6 months [25]. Several retrospective studies have reported a median survival time of 5.4–11.4 months for NSCLC patients with ILD treated with chemotherapy [15–19]. In this study, the median survival time of patients was similar to that reported in previous studies. Compared with NSCLC patients without ILD treated with platinum-based chemotherapy (median OS; 11–15 months), the prognosis of those with ILD is poor [20, 21].

To the best of our knowledge, the present study is the first to evaluate prognostic factors for NSCLC patients with ILD treated with platinum-based chemotherapy. The results of this study showed that clinical stage was an independent prognostic factor for NSCLC patients with ILD. Although standard treatment for clinical stage III NSCLC patients is chemoradiotherapy, the safety of thoracic radiotherapy

Table 5 Univariate and multivariate analysis of prognostic factors for NSCLC patients with ILD treated with platinum-based chemotherapy ($N = 104$)

	Univariate analysis		Multivariate analysis	
	HR (95 % CI)	*p* value	HR (95 % CI)	*p* value
Gender				
Male	0.699 (0.324–1.822)	0.4290	0.689 (0.307–1.843)	0.4267
Female				
Age				
<70	0.955 (0.622–1.491)	0.8355	0.889 (0.553–1.446)	0.6312
≥70				
ECOG-PS				
0–1	0.689 (0.352–1.553)	0.3412	0.617 (0.300–1.438)	0.2447
2				
Histology				
Squamous	0.845 (0.550–1.286)	0.4332	0.772 (0.494–1.193)	0.2446
Non-squamous				
CT pattern				
Non-UIP	0.969 (0.612–1.499)	0.8902	0.679 (0.394–1.141)	0.1451
UIP				
Clinical				
Stage IIIA–IIIB	0.611 (0.393–0.936)	0.0233	0.524 (0.320–0.850)	0.0087
IV/recurrence after surgical resection				

ILD interstitial lung disease, *PS* performance status, *NSCLC* non-small cell lung cancer, *CI* confidence interval, and CT computed tomography

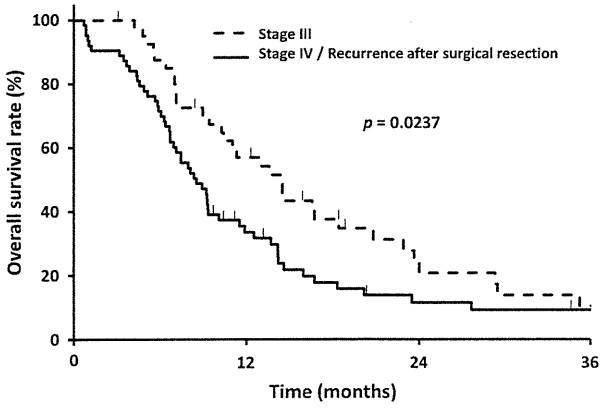

Fig. 2 Overall survival curve for 41 NSCLC patients with ILD diagnosed as clinical stage III and 63 NSCLC patients as stage IV or recurrence after surgical resection. *OS* overall survival, *NSCLC* non-small cell lung cancer, and *ILD* interstitial lung disease

for stage III NSCLC patients with ILD remains unclear. However, some reports suggest that ILD is a risk factor for severe radiation pneumonitis [22, 23]. Therefore, in clinical practice, most physicians avoid thoracic radiotherapy for lung cancer patients with ILD and instead select only chemotherapy.

The optimal chemotherapy regimen for NSCLC patients with ILD remains unclear because of the lack of randomized trials. Based on the results of a prospective study by Minegishi et al. [24] and our previous retrospective study [12], we frequently observed the use of the combination of carboplatin with paclitaxel for advanced NSCLC with ILD. However, another study reported risks associated with carboplatin and paclitaxel for NSCLC patients with ILD [15]. In addition, an optimal platinum-based chemotherapy regimen for NSCLC patients without ILD remains unclear [20, 25]. According to recommended treatment strategies for NSCLC patients without ILD, platinum-based chemotherapy regimens are often used for NSCLC patients with ILD in clinical practice. In this study, during first-line platinum-based chemotherapy, 9 % of NSCLC patients developed chemotherapy-related exacerbation of ILD. However, 67 % of these cases occurred during the second or subsequent line of chemotherapy. It is also very important to identify an optimal treatment regimen for previously treated NSCLC patients with ILD, because docetaxel and pemetrexed can reportedly lead to drug-induced pneumonitis in patients with preexisting ILD [26, 27].

A major limitation to this retrospective analysis was that only 104 patients treated at a single institution were evaluated. However, previous reports evaluated less than 70 patients, and this study included mostly NSCLC patients with ILD. The diagnosis of ILD and exacerbation of ILD were based on CT findings and not on histological examinations. The American Thoracic Society/European Respiratory Society consensus statement also described criteria for the clinical diagnosis of idiopathic pulmonary fibrosis according to CT findings [28].

In conclusion, the results of our study suggest that the prognosis of NSCLC patients with ILD is worse than that

of NSCLC patients without ILD. Furthermore, the risk of exacerbation of ILD in patients treated with platinum-based chemotherapy as the first-line treatment was slightly lower than that reported in previous studies.

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

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Implementation status and explanatory analysis of early advance care planning for Stage IV non-small cell lung cancer patients

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Abstract

Objective: The American Society of Clinical Oncology published the goals of individualized care including advance care planning for advanced cancer patients in 2011. However, no data are available on the implementation status of advance care planning.

Methods: We retrospectively reviewed the electronic medical records and informed consent forms of consecutive Stage IV non-small cell lung cancer patients treated with chemotherapy between January 2010 and December 2012 at our institution. Two outcomes were defined to investigate the advance care planning implementation status: C–D, the duration from the last day of chemotherapy to death and D–D, that from the day of confirmed do-not-attempt-resuscitation order to death.

Results: The study included 136 eligible patients. The advance care planning implementation status in participating patients was as follows: 96 (70%) patients received information on 'incurable disease before first-line chemotherapy', 69 (50%) were informed about 'supportive care before first-line chemotherapy', whereas 43 (32%) learned about their prognosis. The do-not-attempt-resuscitation decision was reflected in 29 patients' will (21%). The median C–D was 64 days. Receipt of ≤2 chemotherapy regimens and provision of prognosis information to patients were significantly associated with long C–D in multivariate analysis. The median D–D was 25 days. Provision of information on supportive care before first-line chemotherapy and provision of prognosis information to patients were significantly associated with long D–D in multivariate analysis.

Conclusions: Our results suggest that there is possible benefit from providing information on supportive care before first-line chemotherapy and informing patients about their prognosis in prolonging the duration of supportive care.

Key words: advance care planning, lung cancer, do-not-attempt-resuscitation, prognosis, supportive care

Introduction

Advance care planning (ACP) is a process whereby a patient, in consultation with healthcare providers, family members and significant others, decides on the future goals of his/her end-of-life (EOL) care by defining goals and expectations (1). Physicians can play an important role by informing patients about ACP, directing them to appropriate resources, counseling them as they engage in ACP and assisting in tailoring their advance directives for prognosis. A randomized controlled trial (RCT) targeting elderly patients reported that ACP improves EOL care and patients' and families' satisfaction, while reducing stress, anxiety and depression among surviving relatives (2).

Patients with advanced incurable cancer face complex physical, psychological, social and spiritual consequences of the disease and its treatment (3). Care for these patients should therefore include an individualized assessment of each patient's needs, goals and preferences throughout the disease course. Consideration of disease-oriented therapy, symptom management and quality of life (QOL) is an important aspect of quality cancer care. In the Phase I clinic at MD Anderson Cancer Center, ~20% of participants did not discuss ACP (4). However, ~42% of patients reported having a living will, 46% had a medical power of attorney and 19% had a do-not-attempt-resuscitation (DNAR) order.

Current guidelines recommend that discussions on EOL care planning begin early in the disease course for patients with incurable cancer (3,5–9). The Cancer Outcomes Research and Surveillance Consortium (CanCORS) reported that, of 1213 lung cancer patients who died at the end of the abstraction period, 1064 (88%) discussed EOL care, defined as a discussion on a DNAR order and venue for dying (10). On the other hand, of 322 lung cancer patients who were alive at the end of the abstraction period, 148 (46%) discussed EOL care (10). In addition, among 959 patients with documented EOL care discussions who died during follow-up, discussions took place at a median of 33 days before death (10).

The American Society of Clinical Oncology (ASCO) published the goals of individualized care for advanced cancer patients in 2011 (ASCO statement) (3). Table 1 summarizes the key elements of individualized care for patients with advanced cancer (3). However, no data are available on the implementation status of these key elements. Thus, we investigated them as the ACP implementation status and analyzed explanatory factors associated with ACP outcomes.

Table 1. Key elements of individualized care for patients with advanced cancer

1. Patients should be well informed about their prognosis and treatment options, ensuring that they have opportunities to make their preferences and concerns regarding treatment and supportive care known.
2. Anticancer therapy should be discussed and offered when evidence supports a reasonable chance of providing meaningful clinical benefit.
3. Options to prioritize and enhance patients' quality of life should be discussed at the time advanced cancer is diagnosed and throughout the course of illness along with development of a treatment plan that includes goals of therapy.
4. Conversations about anticancer interventions should include information on likelihood of response, the nature of response and the adverse effects and risks of any therapy. Direct costs to the patient in terms of time, toxicity, loss of alternatives or financial impacts that can be anticipated should also be discussed to allow patients to make informed choices.
5. Whenever possible, patients with advanced cancer should be given the opportunity to participate in clinical trials or other forms of research that may improve their outcomes or improve the care of future patients.
6. When disease-directed options are exhausted, patients should be encouraged to transition to symptom-directed palliative care alone with the goal of minimizing physical and emotional suffering and ensuring that patients with advanced cancer are given the opportunity to die with dignity and peace of mind.

Patients and methods

Patient selection

We retrospectively reviewed the electronic medical records and informed consent forms of consecutive non-small cell lung cancer (NSCLC) patients who were diagnosed with Stage IV disease, received chemotherapy and died between January 2010 and December 2012 at our institution. Treatments included platinum-based chemotherapy, single-agent chemotherapy and therapy with epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKI). Concurrent palliative thoracic radiotherapy and platinum-based chemotherapy were allowed. This study was approved by the institutional review board of Shizuoka Cancer Center (approval date: 25 June 2013; approved #: 25-J38-25-1-3). Written informed consent was not required because this study is retrospective.

Evaluation and outcomes

We referred to the key elements of the ASCO statement when evaluating the ACP implementation status. Items selected for investigation included provision of information to patients on incurable disease and supportive care before first-line chemotherapy, chemotherapy risks and benefits and chemotherapy expenses and prognosis. The mean of 'supportive care' before first-line chemotherapy was the optional treatment otherwise chemotherapy. In the case of providing information of prognosis before first-line chemotherapy, prognosis was defined as median survival time. On the other hand, in the case of providing information of prognosis after best supportive care (BSC) to mainly family members only, prognosis was defined as life expectancy. Other items included providing information and facilitating participation in clinical trials of chemotherapy, confirming the existence of a DNAR order and determining the existence of a living will.

The implementation status of ACP was investigated on the basis of two outcomes: duration from the last day of chemotherapy to death (C–D) and that from the day of confirmed DNAR order to death (D–D). In addition, we examined the timing and conversation targets, whether they should be patients and family members, patients only or family members only, for provision of information on patients' prognosis and confirming the DNAR order. Overall survival (OS) was measured from the start of first-line chemotherapy to the date of death. There were no cases of censored data because the target population was patients who died.

Statistical analyses

OS, C–D and D–D were estimated using the Kaplan–Meier method. Explanatory factors associated with C–D and D–D were analyzed using Cox regression analysis. We chose explanatory factors for which we assessed the clinical significance, and two-sided P values were considered significant when values were <0.20 in univariate analysis. In multivariate analysis, two-sided P values of <0.05 were considered statistically significant. All analyses were performed using JMP 9 software (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

A total of 136 patients were eligible for this study. Patient characteristics are listed in Table 2. Patient age ranged from 37 to 93 years (median, 67 years). The patient cohort comprised 89 men (65%) and 47 women (35%). One hundred and five (77%) patients had a current smoking status or a history of smoking. The most predominant histological type was adenocarcinoma (103 patients, 76%), followed by squamous cell carcinoma (19 patients, 14%) and other histological types (14 patients, 10%). EGFR mutation status was investigated in 118 patients. Of these, 30 with adenocarcinoma had a sensitive mutation and 88 had a wild-type genotype, including three with minor mutations and one with an anaplastic lymphoma kinase (ALK) fusion gene. At the first visit, 110 patients had an Eastern Cooperative Oncology Group performance status (PS) of 0–1, 2 had a PS of 2 and 15 had a PS of 3.

Treatment and OS

Seventy-one patients received only one regimen, 39 received two and 26 received more than three. As first-line chemotherapy, 46 patients received cisplatin-based agents, 33 received carboplatin-based agents (10 of whom also received bevacizumab) and 23 received single-agent chemotherapy. Of the29 patients treated with EGFR-TKI, 3 had a non-sensitive mutation and 1 had wild-type *EGFR*. Five patients received concurrent chemoradiotherapy. As last-line chemotherapy, 92 patients received intravenous chemotherapy, 10 received oral cytotoxic argents, 33 received EGFR-TKI and 1 received ALK-TKI. The median survival time of all patients was 7.5 months (95% confidence interval, 6.5–8.7 months).

ACP implementation status

The ACP implementation status is summarized in Table 3. Information provided before first-line chemotherapy was on 'incurable disease' in 96 (70%) patients, 'supportive care' in 69 (50%) patients, 'chemotherapy risks and benefits' in 116 (85%) patients and 'chemotherapy expenses' in 16 (12%) patients. Of the 48 (35%) patients who were informed about 'clinical trials', 23 enrolled in these trials.

Information on prognosis

Forty-three (32%) patients were informed about their prognosis during their disease course. The timing of prognosis information provision is summarized in Table 4. Among 75 patients with their prognosis informed to family members only, such information was provided before and during first-line chemotherapy in 30 (40%) patients and after BSC was indicated as the treatment strategy in 25 (33%) patients. On the other hand, of 35 patients with prognosis informed to both patients and family members, 29 (83%) received such information before and during first-line chemotherapy. Prognosis information was relayed to patients only in eight patients, six before and two during first-line chemotherapy.

Confirmed DNAR

During the entire disease course, a DNAR order was confirmed by 12 (9%) patients. The timing of DNAR order confirmation is also summarized in Table 4. Among 121 patients with a DNAR order confirmed by family members only, confirmation occurred before and during first-line chemotherapy in 27 (22%) patients and after defining BSC as the treatment strategy in 64 (53%) patients. Furthermore, of the 11 patients with the DNAR order confirmed by both patients and family members, 2 (18%) were confirmed before and during first-line chemotherapy. One patient confirmed the DNAR order at the time of disease progression. The DNAR order was reflected in 29 (21%) patients' wills.

Explanatory analysis

The median C–D in all patients was 64 days (range, 0–614 days). When stratified by the last-line chemotherapy, the median C–D was 72 days (range, 6–614 days) for 92 patients who received intravenous chemotherapy, 40 days (range, 5–247 days) for 10 patients who received oral cytotoxic argents and 50 days (range, 0–524 days) for 34 patients who received TKI. In multivariate analysis, receipt of ≤2 chemotherapy regimens and provision of prognosis information to patients were significantly associated with long C–D for all patients (Table 5). The median D–D was 25 days (range, 0–371 days). Provision of information regarding supportive care before first-line chemotherapy and provision of prognosis information to patients were significantly associated with long D–D in multivariate analysis (Table 6).

Discussion

To the best of our knowledge, the present study is first to investigate the ACP implementation status before first-line chemotherapy with reference to the ASCO statement. Furthermore, we analyzed

Table 2. Patient characteristics

		N = 136
Age	Median (range), years	67 (37–93)
Sex	Male/female	89/47
Smoking status	Ever/never	105/31
Histology	Ad/Sq/other	103/19/14
EGFR	Mutant/wild-type/unknown	30/88[a]/18
ECOG-PS	0/1/2/3–	29/81/11/15
Number of chemotherapy regimens	1/2/3–	71/39/26

Ad, adenocarcinoma; Sq, squamous cell carcinoma; EGFR, epidermal growth factor receptor; ECOG-PS, Eastern Cooperative Oncology Group performance status.

[a]EGFR minor mutation = 3; anaplastic lymphoma kinase = 2.

Table 3. Advance care planning implementation status

	Yes (%)	No
Information provided		
Incurable disease, before first-line chemotherapy	96 (70)	40
Supportive care, before chemotherapy	69 (50)	67
Chemotherapy risks and benefits	116 (85)	20
Chemotherapy expenses	16 (12)	120
Prognosis	43 (32)	93
Clinical trial		
Informed	48 (35)	88
Participated	23 (17)	113
Confirmed DNAR	133 (98)	3
By the patient	12 (9)	–
Living will	25 (18)	111

DNAR, do-not-attempt-resuscitate.

Table 4. The timing of informed prognosis and confirmed DNAR

	N	Before first-line chemotherapy	During chemotherapy	PD	BSC-	PCU-
Prognostic information provision	118					
Only family members	75	30	7	13	22	3
Patients and family members	35	25	4	2	4	0
Only patients	8	6	1	1	0	0
Request for prognostic information	51					
Only family members	13	6	0	1	6	0
Patients and family members	11	8	1	0	2	0
Only patients	27	18[a]	4	2	3	0
Confirmed DNAR	133					
Only family members	121	14	13	30	53	11
Patients and family members	11	1	1	3	6	0
Only patients	1	–	–	1	–	–

PD means at the time of PD. BSC- means from the time treatment strategy involves BSC only to the time of death or entering PCU. PCU- means the period between entering PCU and death.

PD, progressive disease; BSC, best supportive care; PCU, palliative care unit.

[a]Two patients were not provided with prognostic information.

Table 5. Univariate and multivariate analyses of explanatory factors for advance care planning implementation status associated with the duration from the last day of chemotherapy to death

	Univariate analysis		Multivariate analysis	
	P value	HR	95% CI	*P* value
Age (≥75 years/<75 years)	0.11	0.66	0.40–1.05	0.08
PS (0–1/≥2)	0.08	0.68	0.40–1.19	0.18
EGFR (sensitive mutation/wild-type or unknown)	0.20	1.06	0.64–1.69	0.81
Number of regimens (≤2/>2)	0.02	0.40	0.24–0.68	<0.01
Supportive care, before chemotherapy (yes/no)	0.86	1.05	0.73–1.51	0.78
Prognostic information provision	0.14			0.02
Only family members		1		
Including patients		0.58	0.37–0.89	
Not provided		0.63	0.35–1.06	
Confirmed DNAR from patients or their living will (yes/no)	0.94	1.17	0.74–1.80	0.47

CI, confidence interval; EGFR, epidermal growth factor receptor; PS, performance status; HR, hazard ratio.

Table 6. Univariate and multivariate analyses on explanatory factors for advance care planning implementation status associated with the duration from the day of a confirmed DNAR order to death

	Univariate analysis	Multivariate analysis		
	P value	HR	95% CI	*P* value
Age (≥75 years/<75 years)	0.84	1.13	0.70–1.76	0.58
PS (0–1/≥2)	0.06	1.65	0.97–2.92	0.06
EGFR (sensitive mutation/wild-type or unknown)	0.21	0.80	0.47–1.29	0.37
Number of regimens (≤2/>2)	0.36	0.85	0.53–1.39	0.51
Supportive care, before chemotherapy (yes/no)	0.13	0.61	0.42–0.88	<0.01
Prognostic information provision	0.06			0.01
Only family members		0.51	0.30–0.90	
Including patients		0.36	0.19–0.71	
Not provided		1		
Confirmed DNAR from the patients or their living will (yes/no)	0.09	0.98	0.61–1.52	0.94

explanatory factors associated with two defined outcomes of the ACP implementation status. The median C–D was 64 days. Receipt of ≤2 chemotherapy regimens and provision of prognosis information to patients were significantly associated with long C–D in multivariate analysis. The median D–D was 25 days. Provision of information regarding supportive care before first-line chemotherapy and provision of prognosis information to patients were significantly associated with long D–D in multivariate analysis.

The Phase I clinic at MD Anderson Cancer Center conducted a questionnaire survey on advance directives (living wills and medical powers of