SPANDIDOS PUBLICATIONS

MOLECULAR AND CLINICAL ONCOLOGY 10: 541-546, 2019

Paclitaxel for relapsed small-cell lung cancer patients with idiopathic interstitial pneumonias

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Received December 20, 2018; Accepted March 13, 2019

DOI: 10.3892/mco.2019.1828

Abstract. Although first-line chemotherapy is highly sensitive against small-cell lung cancer (SCLC), most patients subsequently experience disease progression. Topotecan is the standard therapy for sensitive-relapsed SCLC patients, and subgroup analysis of a randomized phase III trial suggests that amrubicin is effective for refractory-relapsed SCLC. However, because of the lack of the evidence based on clinical trials, the effectiveness of systemic chemotherapy for relapsed SCLC patients with idiopathic interstitial pneumonias (IIPs) is unclear. In the presentstudy, 17 relapsed SCLC patients with IIPs who received a paclitaxel (PTX)-containing regimen as a second-line chemotherapy were retrospectively reviewed. The overall response rate and the disease control rate of the PTX-containing regimens were 29.4 and 47.1%, respectively. The median progression-free survival and the overall survival of the regimens were 2.7 months [95% confidence interval (CI), 1.6-3.6 months] and 3.6 months (95% CI, 2.3-14.0 months), respectively. Grade 3-4 neutropenia and febrile neutropenia occurred in 12 (70.6%) and 2 (11.8%) patients, respectively. During the treatment period, acute exacerbation (AE) of IIPs was observed in five patients (29.4%). Treatment-associated fatality was observed in 1 patient with febrile neutropenia and in 1 patient with AE of IIPs. PTX had promising anti-tumor activity against refractory-relapsed SCLC with IIPs. However, the survival benefit of the treatment was limited because of the high incidence of AE of IIPs and treatment-related death.

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Key words: small-cell lung cancer, idiopathic interstitial pneumonias, acute exacerbation of idiopathic interstitial pneumonia, paclitaxel, second-line chemotherapy

Introduction

Small-cell lung cancer (SCLC) is a high-grade neuroendocrine lung cancer and comprises about 15% of all lung cancers (1). SCLC is characterized by rapid growth and early metastasis to distant organs, and most patients are diagnosed with extensive disease. Systemic chemotherapy is the standard treatment, and the response rate to first-line platinum-based chemotherapy is high. However, most patients experience disease progression while on or after first-line chemotherapy (2). The response of second-line chemotherapy depends on the interval time from the last day of first-line chemotherapy to the day of confirmed relapse: Sensitive disease (the interval >90 days) has an overall response rate (ORR) of approximately 25% and refractory disease (the interval <90 days) has an ORR of approximately 10% (3,4). Topotecan is safe and effective for the sensitive disease (5,6). Subgroup analysis of a phase III trial suggested the effectiveness of amrubicin for patients with the refractory disease (7). Furthermore, a recent study demonstrated the antitumor activity with durable response of immune-checkpoint inhibitors, nivolumab monotherapy and nivolumab plus ipilimumab in patients with both sensitive and refractory disease (8). However, patients with severe complications including idiopathic interstitial pneumonias (IIPs) were excluded from these clinical trials, and therefore the survival benefit of chemotherapy for SCLC patients with IIPs is unclear.

IIPs are a common comorbidity of lung cancer and affect 5.8% of surgically-resected lung cancer patients (9). Among patients with IIPs, the prevalence of lung cancer at the diagnosis of IIPs was 6-17% (10). The presence of IIPs is an obstacle to systemic chemotherapy because of the risk of death and the deterioration of quality of life attributed to acute exacerbation (AE) of IIPs (11). A combination of platinum agents, cisplatin or carboplatin, plus etoposide is the standard treatment regimen for chemotherapy-naïve SCLC patients with extensive disease (2,3). The safety and efficacy of these regimens for SCLC patients with IIPs or interstitial lung disease were evaluated in two retrospective studies and one prospective study in Japan. AE related to platinum agents plus etoposide was observed in 5.9% (1/17) of patients with IIPs and 1.9% (1/52) of patients with preexisting interstitial

lung disease (12,13). The ORRs, the median progression-free survival (PFS), and the median survival time (MST) of the combination of platinum agents plus etoposide for SCLC patients with IIPs were 63.6-88.2%, 4.5-5.5 months, and 7.0-9.4 months, respectively (12-14). Compared to the MST of SCLC patients who received only supportive care, which is 2-3 months (15), these results reveal the benefit of first-line chemotherapy for SCLC patients with IIPs. In the second-line setting, topotecan-induced AE occurred in 20.0-23.8% of SCLC patients with interstitial lung disease (16,17). Two retrospective studies reported that the incidences of amrubicin-induced AE were 10% (1/10 patients) and 17.6% (3/17 patients) in lung cancer patients with preexisting interstitial lung disease (13,18). Thus, the standard chemotherapy regimens for relapsed SCLC may be ineligible for patients with IIPs because of the high incidence of AE.

The efficacy of single agent paclitaxel (PTX) for previously treated SCLC patients was assessed in two phase II studies, and the ORRs of PTX were 23.8 and 29.2% (19,20). PTX in combination with carboplatin is a candidate regimen for advanced non-small cell lung cancer (NSCLC) patients with IIPs in terms of the low incidence of AE (21). Furthermore, a retrospective study suggested the safety and effectiveness of second-line chemotherapy including PTX in relapsed SCLC patients with IIPs (16). Thus, these results suggested that PTX may be a treatment option for relapsed SCLC patients with IIPs. However, no study has examined the safety and efficacy of PTX in relapsed SCLC patients with IIPs. Therefore, we conducted a retrospective analyses to evaluate the safety and efficacy of PTX in relapsed SCLC patients with IIPs.

Materials and and methods

Study population and design. Between January 2010 and August 2017, we enrolled 32 patients (all Japanese) who were diagnosed with both SCLC and IIPs and received first-line chemotherapy at Tokushima University hospital. Of the 32 patients, three died during first-line chemotherapy: Two died from tumor-progression and another died from respiratory infection following febrile neutropenia. They were excluded from the analysis. We retrospectively analyzed clinical features including age, sex, smoking history, performance status (PS), and clinical stage at the end of first-line chemotherapy. Radiologic features of IIPs on high-resolution computed tomography (HRCT) and respiratory function test at the diagnosis of SCLC were also analyzed. The clinical stage was determined on the basis of the international TNM criteria for cancer staging. PS was assessed according to the Eastern Cooperative Oncology Group (ECOG) classification. The cumulative cigarette exposure (pack-years) was calculated by multiplying the average number of packs of cigarettes smoked per day by the number of years for smoking. The diagnosis of IIPs was made according to the reported criteria (22). IIPs were classified into two groups: Idiopathic pulmonary fibrosis (IPF), which consists of usual interstitial pneumonia (UIP) or a possible UIP pattern by HRCT, and non-IPF, which consists of an inconsistent UIP pattern by HRCT according to the official ATS/ERS/JRS/ALAT statement (23). AE of IIPs was diagnosed using the international working group report (24).

Table I. Comparison of the characteristics of SCLC patients with IIPs.

Variables	PTX *n*=17	BSC *n*=12	P-value
Age (years)			0.365[a]
Mean (SEM)	72.0±2.3	74.8±1.3	
Sex			1.000[b]
Male	16 (94%)	11 (92%)	
Female	1 (6%)	1 (8%)	
ECOG PS			0.119[b]
0, 1	13 (76%)	5 (42%)	
≥2	4 (24%)	7 (58%)	
Clinical stage			0.422[b]
LD	4 (24%)	5 (42%)	
ED	13 (76%)	7 (58%)	
Cigarette exposure (pack-years)			0.477[c]
Mean (SEM)	68.8±10.2	80.3±12.2	
Type of IIPs			1.000[b]
IPF	6 (35%)	5 (42%)	
Non-IPF	11 (65%)	7 (58%)	
Response to first-line therapy			1.000[b]
CR, PR	12 (71%)	9 (75%)	
SD, PD	5 (29%)	3 (25%)	
Type of relapse			0.279[b]
Sensitive	1 (6%)	3 (25%)	
Refractory	16 (94%)	9 (75%)	

[a]Student's t-test with Welch's correction, [b]Fisher's exact test and [c]Student's t-test. SCLC, small cell lung cancer; IIPs, idiopathic interstitial pneumonias; PTX, paclitaxel; BSC, best supportive care; SEM, standard error of mean; ECOG PS, the Eastern Cooperative Oncology Group performance status; LD, limited disease; ED, extensive disease; IPF, idiopathic pulmonary fibrosis; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Statistical analysis. All comparisons between populations were performed by the Fisher's exact test or Student's t-test, as appropriate. ORR was defined using Response Evaluation Criteria in Solid Tumors (25). Disease control rate (DCR) was defined as the proportion of patients with complete response, partial response, and stable disease. Overall survival (OS) was defined as the time from the date of initiation of PTX-containing regimens until the date of death from any cause. PFS was defined as the time from the date of the initiation of PTX-containing regimens until the date of death or evidence of tumor progression. Patients who were alive or no evidence of tumor progression at the time of analysis were censored at the last known date of follow-up. OS and PFS were estimated using the Kaplan-Meier method, and the log-rank test was used to assess differences between groups. Results are reported as the mean ± standard error of mean (SEM). Adverse events were graded using National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. P-values less than 0.05 were considered significant. Statistical analyses

Table II. Response of second-line chemotherapy for SCLC patients with IIPs.

Regimen	*n*	ORR *n* (%)	DCR *n* (%)
PTX	12	3 (25.0)	6 (50.0)
nab-PTX	4	2 (50.0)	2 (50.0)
CBDCA+PTX	1	0 (0)	0 (0)
All	17	5 (29.4)	8 (47.1)

SCLC, small cell lung cancer; IIPs, idiopathic interstitial pneumonias; ORR, overall response rate; DCR, disease control rate; PTX, paclitaxel; nab-PTX, nanoparticle albumin-bound paclitaxel; CBDCA, carboplatin.

Table III. PTX-related adverse events in SCLC patients with IIPs.

Adverse events	*n* (%)
Grade ≥3	
Hematologic	
Leukopenia	7 (47.1)
Neutropenia	12 (70.6)
Anemia	2 (11.8)
Thrombocytopenia	2 (11.8)
Febrile neutropenia	2 (11.8)
Any grade	
Non-hematologic	
Neuropathy	4 (23.5)
Pneumonitis	5 (29.4)

PTX, paclitaxel; SCLC, small-cell lung cancer; IIPs, idiopathic interstitial pneumonias.

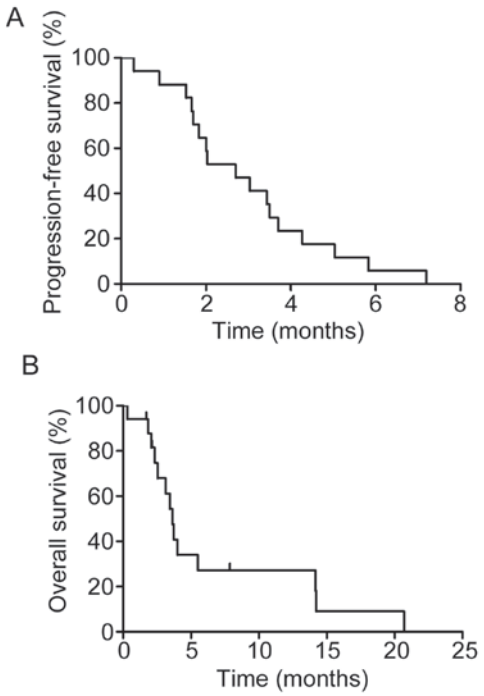

Figure 1. Kaplan-Meier estimates of the probability of progression-free survival and overall survival of PTX for SCLC patients with IIPs. (A) Progression-free survival of PTX for SCLC patients with IIPs (median 2.7 months; 95% CI, 1.6-3.6 months). (B) overall survival of PTX for SCLC patients with IIPs (median 3.6 months; 95% CI, 2.3-14.0 months). PTX, paclitaxel; SCLC, small-cell lung cancer; IIPs, idiopathic interstitial pneumonias; CI, confidence interval.

were performed using GraphPad PRISM (5.01; GraphPad Software, Inc., La Jolla, CA, USA).

Results

Characteristics of SCLC patients with IIPs. We identified 29 SCLC patients with IIPs who received first-line chemotherapy of a platinum-based drug plus etoposide. Of the 29 patients, 17 received PTX-containing regimens (PTX group) and 12 received best supportive care (BSC: BSC group) after disease progression. AE of IIPs related to first-line chemotherapy occurred in one patient in the BSC group. Patients in the BSC group had poor PS compared to those in the PTX group, and the ORR to first-line chemotherapy was similar between the groups (Table I). Of the 17 patients that received PTX, all but one were refractory-relapsed cases; 12 received PTX monotherapy, four received nanoparticle albumin-bound PTX monotherapy, and one received combination therapy with carboplatin plus PTX (Tables I and II).

Efficacy of PTX in SCLC patients with IIPs. During the observation period, 14 patients (82.4%) in the PTX group and 10 (83.3%) patients in the BSC group died. The ORR and the DCR of PTX-containing regimens were 29.4 and 47.1%, respectively (Table II). The median PFS and the MST of PTX-containing regimens were 2.7 months [95% confidence interval (CI), 1.6-3.6 months] and 3.6 months (95% CI, 2.3-14.0 months), respectively (Fig. 1).

Toxicity of PTX in SCLC patients with IIPs. The median number of PTX treatment cycles was two (range 1-7). The most common grade 3-4 adverse events were hematological toxicities in 12 (70.6%) and seven (47.1%) patients with neutropenia and leukopenia, respectively (Table III). Two patients experienced febrile neutropenia (11.8%) and one of them died from respiratory infection. For non-hematologic toxicity, sensory neuropathy of grade 2 or lower and AE of IIPs were observed in four (23.5%) and five patients (29.4%), respectively. The characteristics of five patients that experienced AE of IIPs are summarized in Table IV. All received broad-spectrum antibiotics and high-dose intravenous methylprednisolone pulse therapy followed by oral prednisolone. Four recovered from AE of IIPs, but one died from respiratory failure. No significant factor associated with PTX-induced AE of IIPs was observed (Table V). During the observation period, AE of IIPs was not observed in the BSC group.

Discussion

In this study, we evaluated the safety and efficacy of PTX in relapsed SCLC patients with IIPs and showed that PTX-containing regimens had promising anti-tumor activity

Table IV. The characteristics of patients who developed PTX-induced AE of IIPs.

	Case				
Variables	1	2	3	4	5
Age (years)	67	68	69	69	84
Sex	Male	Male	Male	Male	Female
ECOG PS	2	0	1	1	1
Clinical stage	IVB	IVB	IVB	IVB	IVA
Cigarette exposure (pack-years)	45	64	37	84	20
Type of IIPs	Inconsistent	Inconsistent	UIP	UIP	Inconsistent
History of thoracic radiotherapy	No	No	No	No	No
KL-6 (U/ml)	520	2,210	387	2,107	377
LDH (IU/l)	638	228	346	256	221
CRP (mg/dl)	7.9	0.4	1.5	0.3	0.2
%VC (%)	104.0	86.3	87.9	94.0	56.6
CTCAE Grade	5	3	3	3	3
OS (months)	0.3	2.1[a]	3.4	3.6	4.0

[a]Survivor at the end of follow-up. PTX, paclitaxel; AE, acute exacerbation; IIPs, idiopathic interstitial pneumonias; ECOG PS, the Eastern Cooperative Oncology Group performance status; UIP, usual interstitial pneumonias; KL-6, Krebs von den Lungen-6; LDH, lactate dehydrogenase; CRP, C-reactive protein; VC, vital capacity; CTCAE, Common Terminology Criteria for Adverse Events; OS, overall survival.

against refractory-relapsed SCLC patients with IIPs. However, the survival benefit of PTX in relapsed SCLC patients with IIPs appeared to be limited.

Two phase II studies evaluated the effectiveness of PTX for previously treated SCLC patients without IIPs (19,20), and the ORRs of PTX were 20.0 and 29.2% (19,20). Furthermore, the ORR of PTX with or without carboplatin for both sensitive (39%) and refractory (61%) SCLC patients with IIPs in the second line setting was 27.8% (16). We found that the ORR of PTX-containing regimens in refractory-relapsed SCLC patients with IIPs was 29.4%, which was comparable to previous reports. Because the ORR of second line chemotherapy for refractory-relapsed SCLC patients was 14.8%, PTX may be effective for refractory-relapsed SCLC patients with or without IIPs (4). However, we found that the MST of second-line PTX in refractory-relapsed SCLC patients with IIPs was 3.6 months. The MST of PTX in both sensitive (52%) and refractory (48%) relapsed SCLC patients without IIPs was 5.8 months (20). Furthermore, the MST of second-line chemotherapy including PTX in both sensitive (39%) and refractory (61%) SCLC patients with IIPs was 7.1 months (16). Compared to previous reports, the survival benefit of PTX in this study was limited, which may be because all patients except for one were refractory-relapsed cases.

Severe toxicities related to PTX may also limit the survival benefit of PTX. Grade 3 or higher pneumonitis related to PTX-induced AE of IIPs was observed in five patients (29.4%) and one of them died from respiratory failure in spite of high-dose corticosteroid therapy. AE of IIPs related to second-line PTX was observed in 11% (2/18 patients) of SCLC patients with IPF and at least one of two patients died from pneumonitis (16). In NSCLC patients with IIPs, AE of IIPs related to PTX administered as first-line chemotherapy was observed in 9.5% (10/105 patients), and the incidence of AE of IIPs related to PTX was lower than that related to other agents (21,26-28). Therefore, PTX in combination with carboplatin is a good candidate regimen for NSCLC patients with IIPs. An increased risk of AE of IIPs was observed in lung cancer patients with IIPs that received second- or more-line chemotherapy compared to those that received first-line chemotherapy (13,29). Therefore, the risk of AE of IIPs related to PTX in relapsed SCLC patients may be higher compared to that in NSCLC patients that received PTX as a first-line chemotherapy. Although, we did not find any factors associated with PTX-induced AE of IIPs, UIP pattern was reported to be an independent risk factor for chemotherapy-related AE of interstitial lung disease (ILD) (30). In addition, the baseline serum Krebs von den Lungen-6 (KL-6) level with cut-off values of 1300 U/ml and a disease severity based on the partial pressure of arterial oxygen (PaO_2) were associated with the development of AE of IPF (31,32). Consistent with a previous study, baseline serum KL-6 levels were higher in patients with AE of IIPs than those without AE of IIPs, and all but two patients with baseline serum KL-6 levels above 1300 U/ml developed AE of IIPs. The GAP index helps predicts mortality in patients with IPF (33). A recent study demonstrated that modified GAP index score, which was calculated by four predictors: ILD subtype, sex, age, and forced vital capacity, predicted the risk of AE of ILD associated with chemotherapy in NSCLC patients with ILD (34). The 1-year incidence of AE of ILD in patients with modified GAP index stage I was 14%, and an increased risk of AE of ILD was observed in patients with modified GAP stage II and III. The incidence rate in patients with GAP index stage I was equivalent to that observed in the natural course of IPF patients, and therefore patients with modified GAP index stage I may be indicated for chemotherapy against lung cancer (34). In this study, all five patients who experienced AE of IIPs associated with PTX corresponded to modified GAP

Table V. Comparison of characteristics between SCLC patients with or without PTX-induced AE of IIPs.

Variables	Without AE of IIPs *n*=12	With AE of IIPs *n*=5	P-value
Age (years)			0.779[a]
Mean (SEM)	72.5±3.1	71.0±3.3	
Sex			0.294[b]
Male	12 (100%)	1 (20%)	
Female	0	4 (80%)	
ECOG PS			0.538[b]
0, 1	10 (83%)	3 (60%)	
≥2	2 (17%)	2 (40%)	
Type of IIPs			1.000[b]
IPF	4 (33%)	3 (60%)	
Non-IPF	8 (67%)	2 (40%)	
KL-6 (U/ml)	484.7±87.5	1120.0±424.9	0.217[c]
LDH (IU/l)	265.3±21.5	337.8±78.3	0.422[c]
CRP (mg/dl)	2.7±1.2	2.1±1.5	0.758[a]
%VC (%)	80.5±8.8	85.8±7.9	0.708[a]

[a]Student's t-test, [b]Fisher's exact test and [c]Student's t-test with Welch's correction. SCLC, small cell lung cancer; PTX, paclitaxel; AE, acute exacerbation; IIPs, idiopathic interstitial pneumonias; SEM, standard error of mean; ECOG PS, the Eastern Cooperative Oncology Group performance status; IPF, idiopathic pulmonary fibrosis; KL-6, Krebs von den Lungen-6; LDH, lactate dehydrogenase; CRP, C-reactive protein; VC, vital capacity.

stage II (data not shown). The indication of PTX in relapsed SCLC patients with IIPs should be carefully considered, especially in those with UIP pattern, high baseline serum KL-6 level, low baseline PaO_2, and modified GAP stage II or III.

In this study, grade 3 or 4 neutropenia was observed in 12 (70.6%) of 17 patients. The high incidence of neutropenia was comparable to past clinical trials of weekly PTX or topotecan for relapsed SCLC patients (6,20). Although most adverse events associated with myelosuppression were manageable, one patient died from respiratory infection caused from febrile neutropenia. A clinical trial of weekly PTX for relapsed SCLC patients also reported one case (4.8%) of treatment-related death caused by neutropenic pneumonia (20). When we administer PTX-containing regimens in relapsed SCLC patients, caution is warranted for neutropenia and infection associated with neutropenia.

There were several limitations in the present study. First, this study did not have sufficient power to evaluate the precise clinical benefit of PTX and may have overestimated the incidence of PTX-related AE of IIPs because of the small number of patients and the retrospective nature of the study at a single institution. Second, the diagnoses of IIPs were made clinically with no histological confirmation in all patients. Because SCLC patients usually have no indications for surgery at diagnosis and should receive chemotherapy as soon as possible because of its rapid growth, it is usually difficult to obtain a specimen from non-tumor-bearing fibrotic areas.

In conclusion, this was the first retrospective study to evaluate the safety and efficacy of PTX-containing regimens in relapsed SCLC patients with IIPs. Although PTX-containing regimens demonstrated promising anti-tumor activity against relapsed SCLC with IIPs, the survival benefit was limited because of the high incidence of PTX-related AE of IIPs and treatment-related death. The administration of PTX in relapsed SCLC patients with IIPs should carefully considered and be performed with particular care because of pulmonary toxicity.

Ackonowledgements

Not applicapable.

Funding

No funding was received.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

AS, MH and YN designed the study. AS, HO and KO contributed to the data acquisition. AS, MH, HG and HN analyzed and interpreted the patient data. AS, MH and YN drafted the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Institutional Review Board of Tokushima University Hospital (IRB approval number: 2973). For this type of study formal consent was not required. Information about the current study was disclosed to patients instead of obtaining their written informed consent, and patients who declined to participate were excluded.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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