Feasibility and safety of platinum-doublet therapy in patients with small-cell lung cancer in the third-line setting: A multi-institutional retrospective study

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Abstract. Small-cell lung cancer (SCLC) is a highly malignant tumor, and no standard third-line therapy has been established. The present study retrospectively analyzed the efficacy and safety of platinum-based regimens in patients with third-line SCLC who received third-line chemotherapy. The association of regimen type with overall survival (OS) or time to treatment failure (TTF) was evaluated using the Cox hazard proportional method, including well-known covariates affecting the prognosis of SCLC. TTF and OS analyses were conducted using the Kaplan-Meier method. The data cutoff date was June 30, 2020. As a result, from January 2015 to August 2019, 111 patients were diagnosed with SCLC, and 37 received third-line chemotherapy. Subsequently, 15 patients received a platinum-doublet regimen, and 22 patients received a single-agent regimen. Only the type of regimen was significantly associated with TTF in univariate analysis (odds ratio, 0.44; 95% confidence interval, 0.20-0.95; P=0.03). There were no significant factors associated with OS. The median TTF of patients receiving a platinum-doublet regimen and those receiving a single-agent regimen were 3.9 and 2.3 months, respectively (P=0.03). The overall response rates of the platinum-doublet and single-agent regimens were 20.0 and 4.5%, respectively. Similarly, the disease control rates were 73.3 and 36.4% for platinum-doublet and single-agent regimens, respectively. There was a tendency for adverse events (AEs) with any grade to occur more often in platinum-based regimens compared with in single-agent regimens. Severe AEs of grade 3 or higher were observed more often in the platinum-based regimen, especially in myelosuppression. In conclusion, the present study demonstrated the feasibility and safety of platinum-doublet regimens in patients with SCLC in a third-line setting (Registration no. 2020-048. Date of registration, June 5, 2020).

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Introduction

Small-cell lung cancer (SCLC) is a highly malignant lung tumor that accounts for 10-15% of all lung cancers (1). It is a poorly differentiated tumor immunohistochemically expresses neuroendocrine markers and is characterized by rapid progression, early metastatic spread, and early response to treatment. In the first-line setting, SCLC is highly sensitive to chemotherapy with or without radiotherapy; however, most patients experience relapse within one year after treatment.

Japanese guidelines recommend platinum-doublet therapy with etoposide (VP-16) or irinotecan (CPT-11) as the first-line treatment for extensive stage SCLC and additional immune checkpoint inhibitors have recently become an option (2,3). However, little progress has been made in treating patients with recurrent diseases. In the second-line setting, the time from the completion of first-line therapy to recurrence is considered a prognostic factor. In cases of recurrence later than 90 days after the first-line treatment, we refer to it as 'sensitive relapse' and otherwise as 'refractory relapse' (4). For sensitive relapse, the efficacy of some regimens, including single-agent or combined therapies, has been reported. As for single agents, nogitecan (NGT) and amrubicin (AMR) are included (5-11). Combined chemotherapy consists of cisplatin (CDDP) plus VP-16, CPT-11, or carboplatin (CBDCA) plus VP-16 (12-14). AMR is preferred for refractory relapses (9,11,15). However, there is no recommendation for third-line or later treatments. Compared with non-small cell carcinoma (NSCLC), fewer options are available for SCLC. Therefore, we aimed to explore the efficacy of chemotherapy as a third-line treatment.

Patients and methods

Patients diagnosed with SCLC between January 2015 and August 2019 at Hirosaki University Hospital, Aomori Prefectural Central Hospital, and Hirosaki Central Hospital were retrospectively reviewed. All patients were checked for age, sex, stage (limited or extended), date of last observation and survival, time to treatment failure (TTF), performance status (PS), the existence of metastatic brain tumor, hematological and non-hematological toxicities, and timing of relapse after first-line therapy (e.g., sensitive or refractory). TTF was defined as the time from the start of third-line chemotherapy to the date of treatment discontinuation (all-cause death, disease progression, or all-causal treatment discontinuation, including toxicity or aggravation of general condition). In this study, we adopted TTF, not progression-free survival (PFS) time, because patients who were assessed as having progressive disease not by the Response Evaluation Criteria in Solid Tumors (RECIST) but by the definitive deterioration of clinical symptoms or radiological evaluation were included. All data were analyzed with a cut-off date of June 30, 2020. All categorical variables were analyzed using Fisher's exact test. The primary endpoints were overall survival (OS) and TTF. The association between the type of regimen (platinum-doublet or single-agent) and either TTF or OS was examined using the Cox proportional hazards model. Age, sex, stage, PS, the existence of metastatic brain tumor, and manner of relapse were included as covariates. Significant factors were assessed in the univariate analysis. Toxicity was assessed using the National Cancer Institute Common Toxicity Criteria, version 4.0. P-values are considered to be significant if less than 0.05. Statistical analyses were performed using JMP Pro version 15.2. The study was performed according to the protocol approved by the Ethics Committee of the Hirosaki University Graduate School of Medicine (approval number; 2020-048). As this was a retrospective cohort study, the requirement for informed consent was waived. An opt-out option was conducted on the website of each hospital.

Table I. Comparison of characteristics between two groups.

Characteristic	Platinum-doublet (n=15)	Single-agent regimen (n=22)	P-value
Age, median (range)	64 (46-81)	67 (44-82)	0.33
Sex (male/female)	11/4	17/5	1.00
PS (0-1/≥2)	12/3	19/3	0.67
Manner of relapse Sensitive/ refractory	3/12	8/14	0.47
Disease extent Limited disease/ extensive disease	3/12	5/17	1.00
Brain metastases, n (%)	8 (53)	10 (55)	0.74
Post treatment, n (%)	7 (47)	14 (64)	0.33

PS, performance status.

Table II. Previous treatment regimen in the two groups.

Regimen	Platinum-doublet (n=15)	Single-agent (n=22)
First line		
Platinum + etoposide	9	19
Platinum + irinotecan	6	3
Second line		
Carboplatin + etoposide	2	4
Carboplatin + paclitaxel	2	1
Amrubicin	11	17

Results

Recruitment of patients. Of the 111 patients diagnosed with SCLC between January 2015 and August 2019, 37 received third-line treatment. Fifteen patients received a platinum-doublet regimen, and 22 patients received a single-agent regimen. The patient characteristics are summarized in Table I. No significant differences in age, sex, PS at third-line treatment, disease extent at diagnosis, relapse manner following first-line treatment, the existence of brain metastases, and proportion of patients who could undergo subsequent chemotherapy after third-line treatment failure were found between the two groups. The previous treatments are listed in Table II. As the first-line treatment, VP-16 was the preferred complementary agent for platinum over CPT-11 in our institutions. In the second-line setting, the most commonly used regimen was amrubicin (AMR), followed by CDBCA + paclitaxel (PTX). The third-line treatment regimen is shown in Fig. 1. In the platinum doublet group, CBDCA + VP-16 and CBDCA + PTX accounted for 60 and 40%, respectively. In the single-agent regimen, CPT-11, NGT, AMR, and PTX accounted for 40.9, 40.9, 9.1, and 9.1% of cases, respectively.

Evaluating the endpoint. We evaluated the impact of the type of regimen on the endpoint (TTF or OS) using a Cox proportional hazards model, including covariates. In univariate analysis, only the type of regimen (platinum-doublet) was significantly associated with TTF (odds ratio 0.44 (95% confidence interval 0.20-0.95), P=0.03) (Table III). Thus, we did not conduct a multivariate analysis of TTF. We evaluated the association between regimen type and OS. In the univariate analysis, none of the variables were associated with OS. Subsequently, we evaluated the TTF using log-rank tests for the type of regimen. The median TTF was 2.3 and 3.9 months in single-agent and platinum-doublet regimens, respectively (P=0.03) (Fig. 2).

Efficacy. We also evaluated the efficacy in both groups (Table IV). The platinum-doublet and single-agent regimens' overall response rates (ORR) were 20.0 and 4.5%,

Table III. Association of variables with TTF or OS using Cox proportional hazard model.

	TTF		OS	
Variable	Odds ratio	P-value	Odds ratio	P-value
Sex (male)	0.74 (0.35-1.60)	0.46	1.28 (0.53-3.05)	0.56
Age	1.01 (0.97-1.05)	0.51	1.02 (1.07-0.97)	0.39
Third-line regimen				
Platinum-doublet vs. single-agent	0.44 (0.20-0.95)	0.03	1.41 (0.66-3.00)	0.36
PS at the start of third-line				
0-1 vs. ≥2	1.09 (0.44-2.70)	0.83	0.73 (0.21-2.55)	0.64
Disease extent				
LD vs. ED	0.94 (0.42-2.07)	0.87	0.83 (0.35-1.97)	0.66
Manner of relapse				
Sensitive vs. refractory	0.98 (0.48-2.00)	0.96	0.65 (0.26-1.62)	0.34
Existence of brain metastases				
Yes vs. No	1.45 (0.73-2.85)	0.28	1.29 (0.61-2.71)	0.49

TTF, time to treatment failure; OS, overall survival; PS, performance status; LD, limited disease; ED, extensive disease.

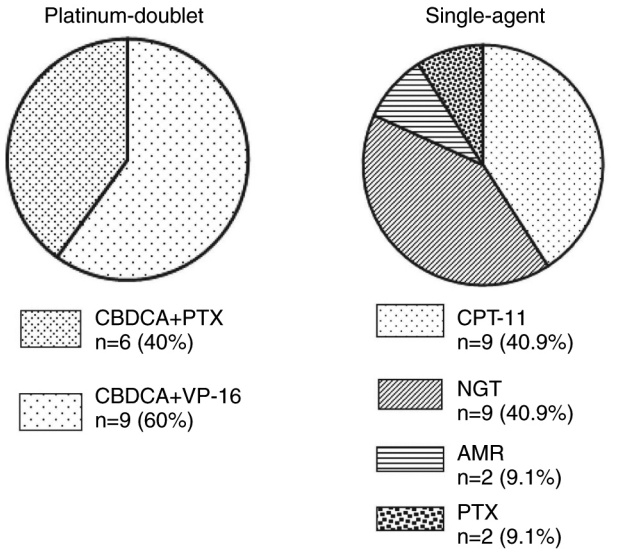

Figure 1. Third-line treatment regimen in platinum-doublet and single-agent groups. CBDCA, carboplatin; PTX, paclitaxel; VP-16, etoposide; CPT-11, irinotecan; NGT, nogitecan; AMR, amrubicin.

respectively. Disease control rates (DCR) were 73.3 and 36.4% for platinum-doublet and single-agent regimens, respectively. In addition, we evaluated the efficacy of the platinum doublet group (Table SI). Six patients received the CBDCA+VP-16 regimen, and nine patients received the CBDCA + PTX regimen. The ORR was 0 and 55.5% in the CBDCA + VP-16 and CBDCA + PTX groups, respectively. The DCRs were 66.7 and 44.4%, respectively.

Toxicity. Concerning treatment-related adverse events (TRAEs), most TRAEs of any grade were more frequent in the platinum-doublet group, except for anorexia, febrile neutropenia, and fatigue (Table V). Severe TRAEs, defined as Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or higher regarding myelosuppression, were more frequent in the platinum-doublet group.

Table IV. Best response following third-line treatment.

Response	Platinum-doublet regimen, n	Single-agent regimen, n
Complete response	0	0
Partial response	3	1
Stable disease	8	7
Progressive disease	4	14
Response rate, %	20.0	4.5
Disease control rate, %	73.3	36.4

Discussion

Most patients with extensive SCLC progress after first-line therapy. The selection of second-line therapy depends on the response to first-line chemotherapy, and the treatment strategy is divided into two types. One is sensitive relapse, and the other is refractory relapse. Generally, sensitive relapse is defined as patients who respond to first-line therapy and relapse more than three months after the completion of first-line chemotherapy. Refractory relapse is defined as relapse within three months (4). This distinction is important because sensitive diseases tend to respond to further systemic therapies, including agents used for first-line chemotherapy. In refractory or recurrent disease, we administer drugs other than those used in first-line therapy (8,16,17). Moreover, there is little evidence supporting the introduction of third-line treatment rather than the best supportive care. There is no recommended drug or combination in the third-line setting

Table V. Adverse events.

	Toxicity, n (%)			
	All		Grade 3≤	
Adverse event	Platinum-doublet regimen	Single-agent regimen	Platinum-doublet regimen	Single-agent regimen
Neutropenia	11 (73.3)	13 (59.0)	4 (26.6)	3 (13.6)
Anemia	11 (73.3)	12 (54.5)	8 (53.3)	6 (27.2)
Thrombocytopenia	10 (66.6)	11 (50.0)	2 (13.3)	1 (4.5)
Febrile neutropenia	0 (0)	2 (9.0)	0 (0)	2 (9.0)
Anorexia	5 (33.3)	13 (59.0)	0 (0)	2 (9.0)
Fatigue	2 (13.3)	7 (31.8)	0 (0)	0 (0)
Constipation	6 (40.0)	5 (22.7)	0 (0)	0 (0)
Neuropathy	5 (33.3)	0 (0)	0 (0)	0 (0)
Pneumonitis	1 (6.6)	1 (4.5)	1 (6.6)	1 (4.5)

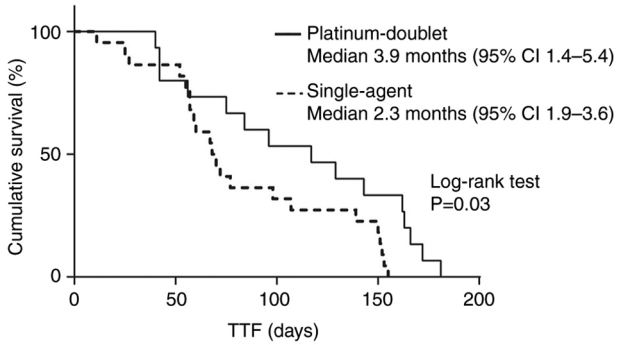

Figure 2. Comparison of TTF between the type of regimen following the third-line using the log-rank test. Median TTF was significantly longer in the platinum-doublet group (3.9 months) compared with in the single-agent group (2.3 months) (P=0.03). TTF, time to treatment failure.

or after that. Given that life expectancy is shorter in patients with SCLC than in those with NSCLC, we assumed that platinum-doublet therapy would be admissible in third-line settings. In the second-line setting, a meta-analysis of the efficacy of platinum-doublet chemotherapy has been reported (18). Most reports have demonstrated that platinum-doublet chemotherapy may be superior to single-agent chemotherapy in terms of OS and PFS. For example, in the second-line setting of sensitive relapse, a phase 3 study on the superiority of CBDCA + VP-16 to NGT in terms of PFS has been recently reported (14). In our analysis, the number of patients who could move to third-line therapy was 24% (27/111), which was similar to the number shown in a previous report (19). In the analysis of the association between treatment regimens and TTF or OS, we included the well-known covariates affecting the prognosis for ED-SCLC, among which only treatment regimen was identified as the significant factor affecting TTF. In our analysis, the platinum doublet demonstrated a relatively high efficacy. In a retrospective analysis of third-line chemotherapy for SCLC, the platinum-doublet regimen tended to improve OS (hazard ratio: 0.84, 95% confidence interval: 0.59-1.19) and ORR (P=0.086) (19). In our analysis, platinum-doublet therapy tended to deteriorate OS in contrast to TTF. OS is likely to be affected by some factors, including pre-and post-treatment complications, such as interstitial lung disease. Therefore, we considered that the platinum-doublet regimen might be the first choice for appropriate patients. In the platinum doublet group, the CBDCA + PTX group showed better ORR and DCR. Meanwhile, in the CBDCA+VP-16 group, all patients except for one received a second dose as a re-challenge setting. Although none of the patients responded to CBDCA+VP-16, the DCR was somewhat high. Considering these results, in third-line settings, the platinum-doublet regimen might play a role in disease control even in the re-challenge setting. Notably, the CBDCA + PTX group demonstrated a high ORR and DCR. The CBDCA + PTX group, which accounted for a large proportion of the platinum-doublet group, might have contributed to the better TTF. In the last few years, there have been reports regarding the efficacy of immune checkpoint inhibitors (nivolumab) for previously treated SCLC. Ready *et al* evaluated patients with SCLC who received nivolumab in the third or later setting in the CheckMate 032 trial. The median PFS and ORR were 1.4 months and 11.9%, respectively (20). Spigel *et al* evaluated the superiority of nivolumab over chemotherapy for OS in a second-line setting (21). However, they could not demonstrate the superiority of nivolumab in terms of OS. PFS and ORR were 1.4 months and 13.7%, respectively. We assume that the high response rate provided by the platinum-doublet regimen might be important for better outcomes in rapidly growing tumors, such as SCLC. The platinum doublet demonstrated good tolerability in the present study, even in a third-line setting. In the above meta-analysis, some studies demonstrated that grade 3 or 4 neutropenia was observed in more than 70% of patients who received the CBDCA plus VP-16 regimen (18). In contrast, the phase 3 study stated above demonstrated that the incidence of any grade 3 or 4 adverse events was less than 30% in the CBDCA plus VP-16 group (14). In our study, grade 3 or 4 neutropenia was relatively less frequent, and grade 3 or 4

thrombocytopenia was more frequent in the platinum-doublet group. We speculated that neutropenia was less frequent in our study because pegfilgrastim was administered to most patients who received a platinum-doublet regimen as primary prevention. However, in late-line settings, careful attention must be paid to adverse events, including myelosuppression. We might be able to consider the platinum-doublet regimen in a third-line setting when the patients are considered to be in good condition and well tolerated.

Our study had some limitations. First, those who could move onto the third-line therapy were very few, which might have been why well-known covariates affecting the prognosis of SCLC were not significant even in univariate analysis. Second, since the present report was a retrospective analysis, it remains unclear whether a platinum-doublet regimen should be administered to all patients. Third, most patients with ED-SCLC receive platinum-doublet chemotherapy plus anti-PD-L1 as the first-line therapy. Therefore, we must address whether platinum-based chemotherapy is feasible for relapsed disease following platinum-based chemotherapy plus anti-PD-L1.

In conclusion, we have demonstrated the feasibility and safety of platinum-based regimens in patients with SCLC in a third-line setting. The platinum doublet regimen might favor some patients who can access third-line treatment. However, this study was only a small retrospective analysis. Currently, because the standard first-line therapy is platinum-based chemotherapy plus anti-PD-L1, we need to explore the feasibility of platinum-based therapy for patients with relapse following platinum-based chemotherapy plus anti-PD-L1.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

TF, TM, and HT conceptualized this study. TF, YT, KC, MI, SS, YH and KO obtained data. TF, TM and HS prepared figures and tables. TF, TM, HT, KT and ST designed the study and drafted the manuscript. KT and ST analyzed the data and provided critical revisions. KO and YH confirmed the authenticity of the raw data. All authors contributed to the manuscript revision and have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Ethical approval for the present study was obtained from the Ethics Committee of the Hirosaki University Graduate School of Medicine (approval no. 2020-048). As this was a retrospective cohort study, the requirement for informed consent was waived. Opt-out was carried out on the Hirosaki University Hospital website.

Patient consent for publication

This was a retrospective study. The requirement for informed consent was waived, and an opt-out option was conducted on the website of each hospital.

Competing interests

The authors declare that they have no competing interests.

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