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Real-World Outcomes with Lurbinectedin in Second Line and Beyond for Extensive Stage Small Cell Lung Cancer in Korea

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Purpose: Small-cell lung cancer (SCLC) accounts for approximately 10–15% of all lung cancers and is characterized by a high recurrence rate, early metastasis, and poor prognosis. Before the FDA approved lurbinectedin for SCLC that progressed on or after platinum-based chemotherapy in 2020, topotecan was the sole second-line option associated with hematological toxicities and modest efficacy. Lurbinectedin received conditional approval in Korea in September 2022 for metastatic SCLC progression, with the same indications. Real-world data on its efficacy remains scarce owing to its recent implementation.

Patients and Methods: Patients with metastatic SCLC who progressed on or after first-line therapy (n = 51) at Yonsei Cancer Center, Seoul, received lurbinectedin at 3.2 mg/m². Efficacy data, including tumor response, progression, survival, and demographics, were recorded.

Results: A total of fifty-one patients received lurbinectedin between April 2023 and March 2024, with thirty-four patients being eligible for the assessment. At diagnosis, approximately one-third of the patients were female, 3% had a poor performance status with an Eastern Cooperative Oncology Group Performance Score (ECOG PS ≥ 2), and the median age was 68. Most patients (80%) had extensive disease. Overall objective response rate (ORR) and disease control rate (DCR) were 20% and 47%, respectively. The median progression-free survival (PFS) was 2.8 months, and the median overall survival (OS) was 3.3 months. Never smokers showed prolonged OS compared with current/former smokers (Smokers; 3.0 vs 7.3 months). Common adverse effects were nausea (53%), loss of appetite (24%), general weakness (18%), anemia (29%), neutropenia (12%), dizziness (6%), alopecia (6%), thrombocytopenia (3%), and pneumonia (3%). Overall, 24% of the patients experienced grade ≥3 adverse events (AEs), with the most common being anemia (9%) and neutropenia (9%).

Conclusion: Real-world data suggest that lurbinectedin is a viable option for patients with SCLC who have progressed on or after platinum-based chemotherapy.

Keywords: SCLC, lurbinectedin, real-world evidence, second line

Introduction

Small-cell lung cancer (SCLC), which accounts for approximately 10–15% of all lung cancers, is characterized by a high recurrence rate, a strong tendency for early metastasis, and poor prognosis.[1] Most patients are diagnosed with extensive disease, with only one-third presenting with early stage disease amenable to potentially curative multimodality therapy.[2] Because SCLC is clinically and biologically distinct from other types of lung cancer, progress in its therapeutic advancement stands in stark contrast to that observed in non-small cell lung cancer (NSCLC).[3,4]

Current evidence suggests platinum-based chemotherapy combined with etoposide and anti-PD-L1 antibody as first-line therapy, although the median OS remains at approximately 1 year even with the addition of atezolizumab.[5,6] This is partly due to the high recurrence rate of the disease, and almost all patients with SCLC relapse after achieving a dramatic

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response to 1st line therapy.[7,8] Before lurbinectedin, a marine-derived selective inhibitor of oncogenic transcription, was approved for metastatic SCLC after first-line therapy in 2020, only a few treatment options were available for SCLC that has progressed after the initial therapy. Among these, topotecan is the most widely used second-line treatment for metastatic SCLC. However, its efficacy was limited, with a median progression-free survival (PFS) of 2.7 months, and topotecan was associated with a significant degree of hematological toxicities[9–12]

Lurbinectedin was approved in Korea in September 2022 for the treatment of adult patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy. However, real-world data on its efficacy is scarce because of its recent implementation.[13–16] In this study, we investigated real-world data of patients with metastatic SCLC treated with lurbinectedin in Korea.

Materials and Methods

Patients and Data Collection

This study enrolled a total of 51 patients treated with lurbinectedin from April 2023 to March 2024. Seventeen patients were unable to be evaluated for response evaluation, and total 34 patients were evaluated. For patients who are classified as "Unable to obtain 1st RECIST", four patients received lurbinectedin but passed away before tumor response evaluation could be completed. One patient discontinued lurbinectedin due to grade 4 general weakness and poor oral intake. Lastly, three patients stopped lurbinectedin based on their personal preferences/beliefs. Patients who are classified as "Follow up loss" were those who did not return to the clinic after receiving lurbinectedin. Lastly, one patient was referred to a hospice care unit before tumor response evaluation (Figure 1). This study was conducted as a retrospective chart review of patients with pathologically confirmed small cell lung cancer (SCLC) who received lurbinectedin beyond first-line therapy at Severance Hospital, Republic of Korea, between April 2023 and March 2024. We excluded patients who received lurbinectedin for indications other than SCLC, such as extrapulmonary small cell cancers.

Efficacy Assessment

Tumor assessments were conducted prior to treatment initiation, and follow-up evaluations were performed via computed tomography within the first three months. Tumor size was measured by investigators in accordance with RECIST 1.1 criteria.[17] Overall response was defined as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). Additional efficacy parameters included the disease control rate, duration of response, PFS, and OS. PFS was defined as the duration from the initiation of lurbinectedin treatment to disease progression or mortality from any cause. OS was defined as the period from lurbinectedin treatment initiation to all-cause mortality.

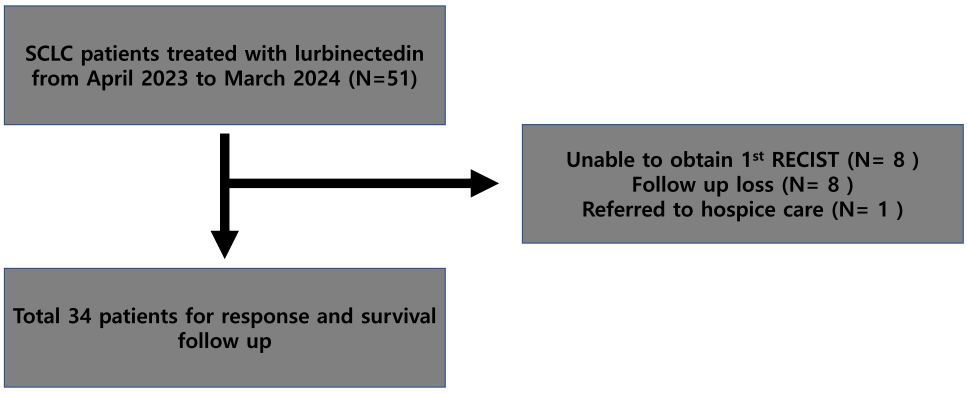

Figure 1 Flow chart of the patients enrolled. Fifty-one patients were initially screened for the study. Seventeen patients did not meet the study criteria and failed to enroll the study. A total of 34 patients were investigated for response and survival outcomes.

Efficacy Comparison with Other 2nd Line Chemotherapies

The comparison of PFS between lurbinectedin and other second-line chemotherapy regimens (topotecan, irinotecan + platinum (IP), and belotecan) was conducted using retrospective data from patients who were treated with chemotherapeutic agents other than lurbinectedin in 2nd lines of therapy but later received lurbinectedin in lines beyond the second, between April 2023 and March 2024. The patient characteristics of each group are described in Tables 1 and 2.

Safety Assessment

Safety was assessed at each patient's visit by routine physical examination and laboratory tests as needed by the physician. Toxicity was classified according to the Common Terminology Criteria for Adverse Events ver. 5 (CTCAE v 5.0). Specifically, we abstracted toxicities, including anemia, neutropenia, thrombocytopenia, fatigue, nausea, anorexia, febrile neutropenia, and an increase in laboratory tests, including creatinine, alanine transaminase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP). Toxicity data, including symptoms such as nausea, fatigue, anorexia, and diarrhea, were extracted from the Electronic Medical Record (EMR).

Statistical Analysis

Data were summarized using descriptive statistics or contingency tables for the demographic and baseline characteristics, response measurements, and safety measurements. The Kaplan–Meier method was used to graphically demonstrate progression free and OS. Statistical analyses were conducted using R studio (Ver 2024.04.1) and GraphPad Prism software (ver 8.0.1).

Ethical Statement

Although the study was retrospective in nature, an informed consent form (ICF) was obtained from all patients before initial treatment. The study protocol adhered to the principles of Good Clinical Practice and was approved by the Institutional Review Board of Severance Hospital (IRB No. 4–2023-0841). The study complied with the Declaration of Helsinki.

Result

Baseline Characteristics

We screened 51 patients with SCLC treated with lurbinectedin between April 2023 and March 2024. A total of 34 patients were eligible for per-protocol analysis (Figure 1). The median follow-up time was 15.8 months (95% confidence interval [CI] 14.6 to 25.76). The median age of all patients was 68 years (range, 42–80 years) and 26 patients (74%) were male. The majority of patients (97%) had an ECOG PS of 0–1, while 1 patient (3%) had an ECOG PS of 2. At the time of initial diagnosis, only 7 patients (20%) had a limited stage, and 27 patients (80%) were in the extended stage. The most common site of metastasis was the brain (53%), followed by the lungs (44%), liver (21%), and bone (18%). Regarding smoking history, 6 patients (18%) were never smokers, 25 patients (74%) were former smokers, and 3 patients (8%) reported themselves as current smokers. In terms of previous therapy history, 18% of the patients received concurrent chemoradiotherapy (CCRT), and only 9% of the patients underwent surgery. Furthermore, 65% of the patients received two or more lines of chemotherapy, ranging from 2 to 4th lines (Table 1).

Efficacy

Within the study population, the median number of lurbinectedin cycles was four (range: 1–16). Specifically, the median number of cycles was 4.5 for second-line patients and 3 for third-line and beyond patients. No patient with CR was recorded for the best objective response rate (ORR) of the study cohort. Partial remission (PR) was observed in 7 patients (20%), stable disease (SD) in 9 (26%), and progressive disease (PD) in 18 (53%). The ORR and disease control rate (DCR) were 20 and 47%, respectively. We analyzed the ORR and DCR in patients who received lurbinectedin as second- or third-line treatment. The ORR was significantly higher in the second-line group compared to the beyond 2nd line group (15% vs 6%, 95% CI 1.2–39.4, $p = 0.03$), whereas no statistically significant difference in DCR was found (18% vs 34%, 95% CI 0.07–2.90, $p = 0.80$) (Table 2).

Table 1 Baseline Characteristics of the Patients

Characteristic	No (n=34, %)
Sex	
Male	26 (74)
Female	8 (26)
Age (yr)	
Median (range)	68 (42–78)
ECOG (PS)	
0–1	33 (97)
>2	1 (3)
Metastasis site	
Adrenal gland	3 (9)
Bone	6 (18)
Brain	18 (53)
Liver	7 (21)
Lung ipsilateral	9 (26)
Lung contralateral	6 (18)
Other	1 (3)
Clinical stage	
LD	7 (20)
ED	27 (80)
Smoking history	
Never	6 (18)
Former	25 (74)
Current	3 (8)
Previous therapy	
Surgery	
Yes	3 (9)
No	31 (91)
CCRT	
Yes	6 (18)
No	28 (82)
Number of previous chemotherapy lines	
1	12 (35)
2	13 (38)

(*Continued*)

Table 1 (Continued).

Characteristic	No (n=34, %)
3	6 (18)
4	2 (6)
5	1 (3)
Previous chemotherapy	
Platinum compound	34 (100)
Etoposide	34 (100)
Atezolizumab	23 (68)
Belotecan	5 (15)
Topotecan	4 (12)
Poly(ADP-ribose) polymerase inhibitor	2 (6)
Cyclophosphamide	2 (6)
Doxorubicin	2 (6)
Vincristine	2 (6)
Tarlatamab	2 (6)

Table 2 Overall Objective Response

	Total (n=34, %)	*p-value*
Objective response rate (ORR)	7 (20)	
ORR (2nd line)	5 (15)	
ORR (≥ 3rd line)	2 (6)	0.03
Disease control rate (DCR)	16 (47)	
DCR (2nd line)	6 (18)	
DCR (>3rd line)	10 (34)	0.80
Best overall response		
CR	0 (0)	
PR	7 (20)	
SD	9 (26)	
PD	18 (54)	
NE	0 (0)	

Notes: Numerical values are presented as percentage (%) or median (range). Objective response rate (ORR) is CR and PR; Disease control rate (DCR) is CR, PR, and SD.
Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

The Kaplan–Meier curves for PFS and OS are shown in Figure 2A and B. The median PFS was 2.8 months, and the median OS was 3.4 months. The median duration of response (DOR) was significantly longer in patients with a chemotherapy-free interval (CTFI) > 90 days compared to those with a CTFI shorter than 90 days (6.70 months vs 2.00 months; 95% CI 0.75–15.1, $p = 0.01$).

Next, we compared PFS and OS according to the lurbinectedin line (Figure 3A and B). The median PFS and OS for 2nd line lurbinectedin was higher compared to the 3rd line lurbinectedin (3.4 vs 2.2 months, 95% CI 0.30–1.15; 4.8 vs 3.3 months, 95% CI 0.29–1.20) although it was not statistically significant. Finally, the PFS of different 2nd line regimens for SCLC from our center was analyzed using retrospective data from patient records. Lurbinectedin was superior to topotecan in terms of median PFS (3.4 vs 1.4 months, 95% CI 0.02–0.81). For irinotecan + platinum (IP) and belotecan, the difference in median PFS was not statistically significant (Figure 4).

Efficacy in Specific Subgroups

We analyzed the ORR and DCR of lurbinectedin according to the smoking history and CTFI (Table S1). There were no statistically significant differences in the ORR and DCR between never-smokers and smokers. However, patients with a CTFI >90 days showed a significantly better ORR than those with a CTFI <90 days (46% vs 14%, $p = 0.027$).

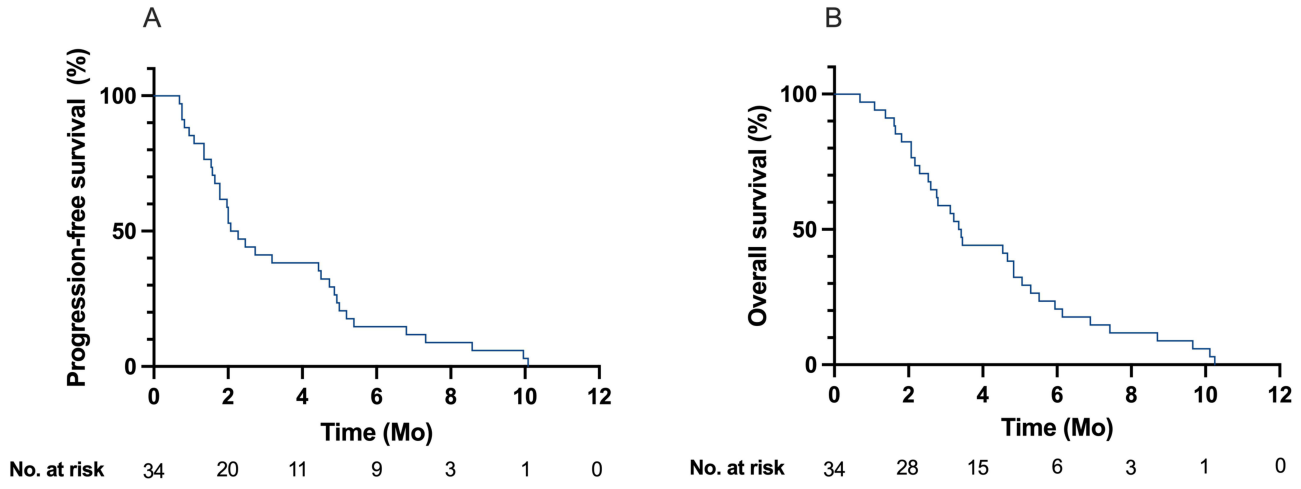

Figure 2 Progression-free survival (**A**) and overall survival (**B**).
Abbreviation: Mo, months.

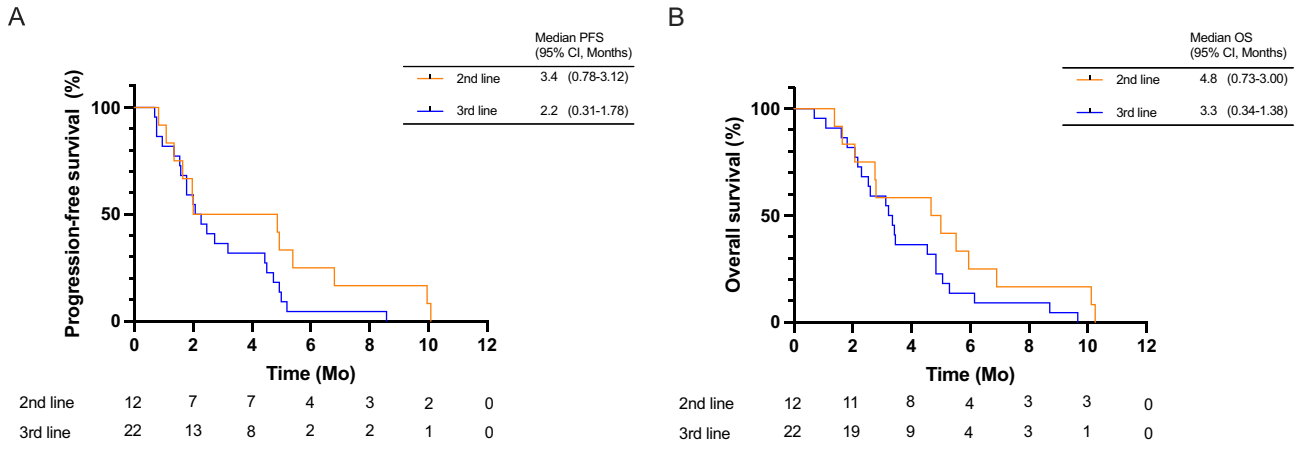

Figure 3 Progression-free survival (**A**) and overall survival (**B**) according to the line of treatment.
Abbreviations: Mo, months; PFS, Progression-free survival; OS, Overall survival.

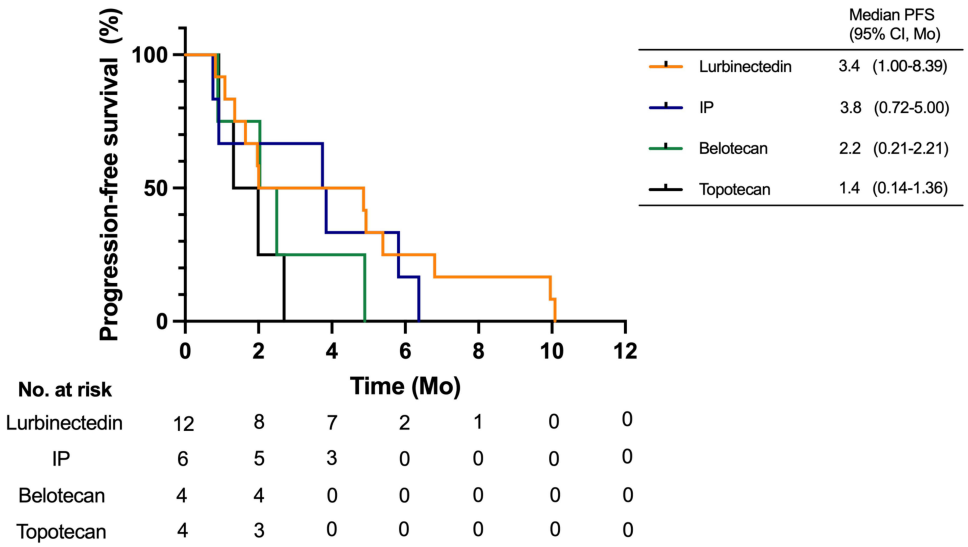

Figure 4 Progression-free survival comparison in different 2nd line treatments. IP, Irinotecan plus platinum-containing lines.
Abbreviations: PFS, progression-free survival; Mo, months; CI, confidence interval.

Next, we analyzed the PFS and OS in patients treated with lurbinectedin who had a history of smoking and CTFI. PFS and OS were analyzed according to smoking history (Figure S1A and B), and we found that although there was no statistically significant difference in PFS (2.0 vs 3.6, 95% CI 0.23–1.34), OS was significantly better in never smokers than in smokers (3.0 vs 7.3 months, 95% CI 0.17–0.99, HR 0.44, $p = 0.03$). We then analyzed whether CTFI affected PFS and OS of patients treated with lurbinectedin in a real-world setting. Patients with longer CTFI had better PFS (2.4 vs 1.9 months, 95% CI 0.37–1.65) and OS (4.1 vs 3.3 months, 95% CI 0.59–2.45) compared to patients with shorter CTFI, although it was not statistically significant (Figure S2A and B).

Cox Proportional Hazard Regression Analysis

Next, we performed Cox proportional hazard regression analysis to assess the role of each clinical parameter on OS and PFS. Cox regression analysis identified older age, male sex, extended disease, brain metastasis, liver metastasis, and a CTFI shorter than 90 days as negative factors for OS (Table 3). Cox hazard regression analysis of PFS showed a trend similar to that of OS, while brain metastasis was not statistically significant (Table S2).

Table 3 Cox Proportional Hazard Regression for OS

	Reference	Cox-regression Analysis		
		Hazard Ratio	95% CI	P val
Age				
<75 yr	≥75	0.93	0.87 to 1.01	0.13
Sex				
Male	Female	6.30	1.91 to 24.8	<0.01
Smoking history				
Never	Former/current	0.98	0.95 to 1.01	0.16

(*Continued*)

Table 3 (Continued).

	Reference	Cox-regression Analysis		
		Hazard Ratio	95% CI	P val
Stages				
LD	ED	0.19	0.05 to 0.72	0.02
Brain metastasis				
Yes	No	0.25	0.01 to 0.65	0.07
Liver metastasis				
Yes	No	8.0	2.17 to 29.08	0.01
CTFI				
<90	≥90	1.1	1.1 to 1.2	<0.01
Line of lurbinectedin				
≤2	>2	0.95	0.60 to 1.50	0.83

Abbreviations: LD, limited disease; ED, extensive disease; CTFI, Chemotherapy free interval.

Safety

Treatment-related AE of any grade and grade 3–4 events were identified in 58% and 24% of patients, respectively. The most common treatment-related AEs were nausea (53%), anemia (29%), and loss of appetite (24%). General weakness was reported in 18% of patients. The most common grade 3–4 AEs were anemia (9%) and neutropenia (9%). Fifteen percent of patients discontinued lurbinectedin, and 3% discontinued permanently due to treatment-related AEs (Table 4). Other notable grade 3–4 treatment-related AEs included pneumonia (3%) and thrombocytopenia, which required hospitalization (3%).

Lastly, we compared G3/G4 AEs with other 2nd line treatments, namely topotecan and belotecan, using previously published data.[10] Although cross-trial comparison should be dealt with caution, compared to topotecan and belotecan, lurbinectedin showed lower incidence of anemia, neutropenia, and thrombocytopenia (Figure 5).

Table 4 Most Common Grade ≥ 3 Treatment-Related AEs

AEs	Grade 1–2, n(%)	Grade 3–4, n(%)
Hematologic		
Anemia	7(20)	3 (9)
Thrombocytopenia	–	1 (3)
Neutropenia	–	3 (9)
Non-hematologic		
General weakness	3(9)	3 (9)
Nausea	18(53)	-
Loss of appetite	8(24)	-
Dizziness	2 (6)	-
Lung infection	-	1(3)
Dyspnea	-	1(3)

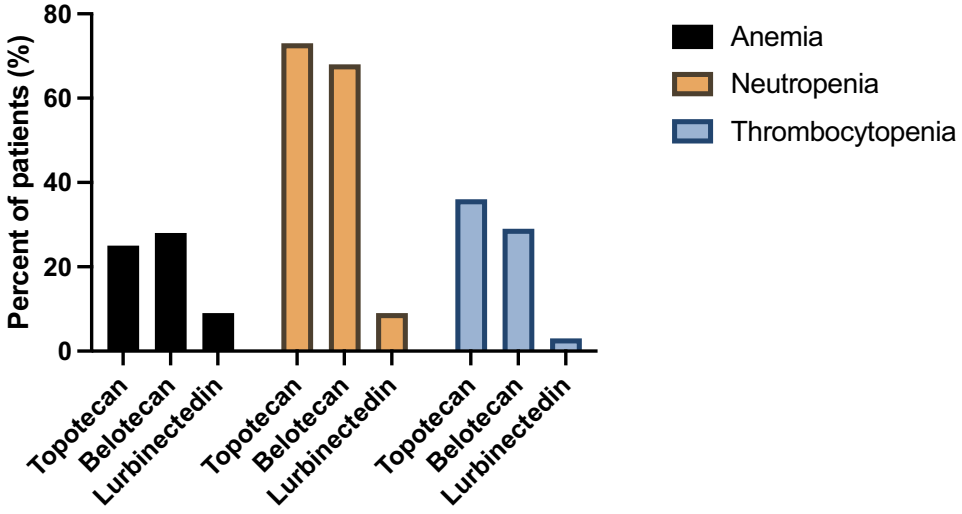

Figure 5 G3/4 hematological toxicities of lurbinectedin, topotecan and belotecan.

Discussion

In this real-world analysis of the efficacy and safety of lurbinectedin in patients with SCLC beyond 2nd line of therapy, the PFS was 2.8 months and OS was 3.4 months, which are comparable to previously reported real-world data.[14,15,18] For instance, real-world outcomes have been demonstrated in a large cohort of patients (n = 396) treated with lurbinectedin, with a median PFS of 2.5 months.[19] Another real-world study of lurbinectedin found that the median PFS is 1.9 months and OS is 2.1 months.[13] Furthermore, the efficacy of lurbinectedin has been reported to be greater in patients with CTFI exceeding 90 days, which aligns with our findings.[20] These safety profiles were comparable to those reported in previous studies.

Unlike the single-arm Phase II basket trial that investigated lurbinectedin as a second-line therapy for SCLC, our data demonstrated shorter PFS and OS.[21] In the phase II trial, the median PFS and OS were 3.5 and 9.3 months, respectively, with the median number of prior therapy lines being 1 and CNS metastasis present only 4% of the patients. In contrast, our patient cohort had median PFS and OS of 2.8 and 3.4 months, a much higher rate of brain metastasis (53%) and was predominantly on 3rd line therapy. This discrepancy may explain the differences of PFS and OS between phase II trial and the real-world data from our center.

Our study demonstrated that Cox regression analysis revealed that a CTFI shorter than 90 days is a negative prognostic factor for OS. PFS and OS were not statistically different according to the CTFI, which is consistent with previous findings.[18] Platinum-sensitive SCLC patients (CTFI > 90) with relapsed disease, platinum re-challenge has been considered a valuable option; however, its usage has been approached with caution due to concerns about cumulative toxicity.[22–24] Additionally, the DOR was significantly longer in patients with a CTFI greater than 90 days than in those with a CTFI of <90 days, highlighting its importance in predicting treatment outcomes with lurbinectedin.

Subgroup analysis showed that patients who received lurbinectedin in 2nd line of therapy had a higher median PFS and OS than those who received lurbinectedin beyond 2nd line of therapy, although this was not statistically significant. We compared the efficacy of lurbinectedin in 2nd line therapy with other drugs, namely topotecan, belotecan, and IP chemotherapy. As previously reported, the median PFS was significantly higher with lurbinectedin than with topotecan, as previously reported.[25] Furthermore, lurbinectedin showed a lower incidence of G3/4 hematological AEs compared to topotecan and belotecan. Before the recent accelerated approval of lurbinectedin by the FDA, the only available treatment options for patients with relapsed SCLC were topotecan and platinum re-challenge. Our results suggest that lurbinectedin has a survival benefit and favorable hematological safety profile compared to topotecan and belotecan, which is in agreement with a recent study.[26]

Our study was limited by its retrospective, single-center design, which included a small number of patients and may introduce selection bias. Data for the safety profile were collected based on self-reported documentation of the symptoms. Therefore, our results may not be generalizable to SCLC patients at other institutions. Other limitations of

this study include overlapping confidence intervals and cross-trial comparisons. However, to our knowledge, this study is the first to analyze the efficacy and safety profile of lurbinectedin in patients with SCLC in Asia.

In summary, the efficacy and safety profiles of lurbinectedin are comparable to those of other real-world data. Our data suggest that lurbinectedin is a viable treatment option for patients with relapsed SCLC.

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Disclosure

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