

Second Line Treatment Choice in Extensive Small Lung Cancer

 Seval Ay,¹  Deniz Tataroglu Ozyukseler,²  Ozgecan Dulgar,³  Muhammed Mustafa Atci,⁴  Rukiye Arikan,⁵
 Ayten Guner Akbiyik,⁶  Mahmut Gumus⁷

¹Department of Medical Oncology, Balıkesir Atatürk City Hospital, Balıkesir, Türkiye

²Department of Medical Oncology, Istanbul Kartal Lutfi Kırdar Training and Research Hospital, Istanbul, Türkiye

³Department of Medical Oncology, Kahramanmaraş Necip Fazıl City Hospital, Kahramanmaraş, Türkiye

⁴Department of Medical Oncology, Haseki Training and Research Hospital, Istanbul, Türkiye

⁵Department of Medical Oncology, Marmara University, Faculty of Medicine, Istanbul, Türkiye

⁶Department of Thoracic Surgery, Medeniyet University, Faculty of Medicine, Istanbul, Türkiye

⁷Department of Medical Oncology, Medeniyet University, Faculty of Medicine, Istanbul, Türkiye

Abstract

Objectives: Small cell lung cancer (SCLC) is approximately 15% of all lung cancer. Topotecan is the preferred chemotherapy regimen in second-line treatment, but toxicity might be limiting to use in clinical routine. Physicians had more experience on weekly paclitaxel due to its easy access and good responses in many cancers. The present study aimed to examine the management of patients treated with topotecan and weekly paclitaxel as second-line treatment of SCLC.

Methods: Patients were divided into two groups due to second-line treatment. The primary endpoint of this study was progression-free survival and overall survival. The secondary endpoint was overall response rate and disease control rate.

Results: The median PFS was 4.5 months (Topotecan 3.7 vs. Paclitaxel 5.5, HR = 0.34, 95% CI: 0.30-0.64, p=0.000) and the median OS was 11 months (Topotecan 9.5 vs. Paclitaxel 12.7, HR = 0.25, 95% CI: 0.20-0.45, p=0.000). ORR was 10.2% in topotecan group and 20.3% in paclitaxel group (p: 0.047). DCR was 15.5% in patients treated with topotecan and 28.8% in paclitaxel group (p=0.033).

Conclusion: The present study compared the currently preferred regimen topotecan with weekly paclitaxel and resulted in better survival and response rates with lower toxicity profile.

Keywords: Small cell lung cancer, second-line treatment, topotecan, weekly paclitaxel, platinum resistance

Cite This Article: Ay S, Tataroglu Ozyukseler D, Dulgar O, Atci MM, Arikan R, Guner Akbiyik A, et al. Second Line Treatment Choice in Extensive Small Lung Cancer. EJMI 2022;6(4):456–461.

Small cell lung cancer (SCLC) is approximately 15% of all lung cancer with the main cause of smoking.^[1] SCLC is high-grade neuroendocrine tumor and is divided into two groups, the limited stage, and the extensive stage.^[2] The limited stage is defined as a tumor limited to one side of the hemithorax with regional lymph node metastases, thus can be treated as a single radiation field. The extensive stage is defined as involvement beyond the limited

disease. SCLC is characterized with short doubling time and nearly 70% of cases are diagnosed in extensive-stage.^[3] Despite high responses in the first-line treatment prognosis of the disease is poor, 2-year survival rates are < 5% and median overall survival is within 8 to 10 months in extensive-stage.^[4]

The standard treatment of extensive stage is a combination treatment of etoposide with cisplatin or carboplatin of

Address for correspondence: Seval Ay, MD. Tibbi Onkoloji Anabilim Dalı, Balıkesir Atatürk Şehir Hastanesi, Balıkesir, Türkiye

Phone: +90 506 483 29 79 **E-mail:** drsevalay@gmail.com

Submitted Date: March 30, 2022 **Accepted Date:** September 06, 2022 **Available Online Date:** September 30, 2022

©Copyright 2022 by Eurasian Journal of Medicine and Investigation - Available online at www.ejmi.org

OPEN ACCESS This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.



four to six cycles. However preferred regimen in the extensive stage includes the programmed death-ligand 1 (PD-L1)-targeted immune checkpoint inhibitors combination with etoposide and platin chemotherapies.^[5, 6] With new treatment strategies, median overall survival reached 12-13 months. Although SCLC is sensitive to platinum-based chemotherapy in the first line, it mostly relapses. The effectiveness of the second-line treatment correlates with the time relapses between the first-line treatment and the relapse. Patients that relapse within 3 months before first-line treatment should not treat to platinum-based treatments and accepted as "platinum-refractory" disease.^[7] Otherwise, some studies accept "platinum-sensitive" disease relapsed >6 months after first-line treatment.^[8]

Guidelines recommend platinum-based chemotherapy combination with immunotherapy as the first-line treatment.^[5, 9] In the second-line treatment and beyond, lots of chemotherapeutic agents are possible options. Topotecan and lurbinectedin are preferred regimens for the subsequent treatment.^[10, 11] Results of the studies using paclitaxel are contradictory. The performance status of patients after first line treatment, might hinder the use of topotecan and usually physicians discontinue the treatment reason of toxicity. Also access to lurbinectedin might be difficult in many centers. Physicians had more experience on weekly paclitaxel due to its easy access and well-known, mostly tolerable side-effects and moderate responses in many cancers. Therefore, the present study aimed to examine the management of patients treated with topotecan or weekly paclitaxel as the second-line treatment of SCLC relapsed <6 months.

Methods

Patient Population

Present study was designed as a retrospective observational study including patients diagnosed with extensive-stage SCLC and receive second-line treatment, from January 2015 to December 2021. Depending on medical records, patients diagnosed with SCLC histology, Eastern Cooperative Oncology Group performance status (ECOG PS) 0 and 1, and progression after the first-line treatment within 6 months were included. Patients <18 years old with non-small cell lung cancer histology, relapsed ≥ 6 months, assessed poor performance status (ECOG 2 or higher) who were unfit for intensive chemotherapy combination and have secondary malignancies were excluded.

The focus of the present study was comparing the efficiency of weekly paclitaxel and topotecan in the second-line treatment of SCLC. Patients were divided into two groups due to second line treatment; first received

topotecan and second received weekly paclitaxel. Age, gender, ECOG PS, body mass index (BMI), and first-line treatment chemotherapy regimens were enrolled from medical records of patients. The primary endpoint of this study was the progression-free survival (PFS) of the second line treatment and the overall survival (OS). PFS was defined as the time interval in months between the start of the second-line chemotherapy and disease progression, death, or last visit if the patient was still alive. OS was calculated from the date of the first diagnosis until the time of death from cancer or the last follow-up time. The secondary endpoint was overall response rate (ORR) and defined as the proportion of patients who have a partial or complete response to therapy and disease control rate (DCR) contain complete, partial, and stable response to the treatment.

Treatment Protocols

Topotecan was administered 1.5 mg/m²/day for 5 days and repeated every twenty-one days until progression. Weekly paclitaxel was received at a dose of 80mg/m² on days of 1,8 and 15 and repeated every 21 days until progression. Patients' toxicities were evaluated by Common Terminology Criteria for Adverse Events (CTCAE) (version 5.0). Doses were modified if needed. Patients who had experienced grade 3 or higher neutropenia were treated with granulocyte colony stimulating- factor (GCS-F).

Statistical Analysis

Quantitative variables were performed by Mann-Whitney U test whereas qualitative variables were carried out by chi square analysis. Survival analyses were calculated by using Kaplan-Meier method and compared with log-rank test. The confidence interval was accepted as 95% and a p-value of <0.05 was set for statistical significance. All statistical analyses were carried out with SPSS statistical software (version 24.0, SPSS Inc., Chicago, IL).

Results

Patients' Characteristics

From January 2015 to December 2021, 130 patients who were diagnosed with SCLC and had received second-line treatment were retrospectively analyzed. Patients were divided into two groups; 71 (54.6%) patients treated with topotecan, and 59 (45.4%) patients treated with weekly paclitaxel as second-line chemotherapy. The topotecan group consisted of 64 males (90.1%) and seven females (9.9%) with a median age of 59 (43-79). In the weekly paclitaxel group, 43 patients were male (72.8%) and 16 female (27.2%) with a median age of 61 (43-79). The median BMI was 25.4 in

topotecan and 24.3 in weekly paclitaxel groups. 27 patients in each group; 38% in the topotecan group and 45.8% in the weekly paclitaxel group were assessed as ECOG-PS 0 whereas 44 patients in topotecan (62%) and 32 patients (54.2%) were ECOG-PS 1. The distribution of first-line treatment was 59 (83.2%) cisplatin plus etoposide, 11 (15.4%) carboplatin plus etoposide and one (1.4%) chemotherapy combination with atezolizumab in the topotecan group. In the weekly paclitaxel group, 45 patients (76.4%) received cisplatin plus etoposide, 20 patients received (20.3%) carboplatin plus etoposide, and two patients (3.3%) received chemotherapy combination with atezolizumab. Baseline patients' clinicopathological characteristics were summarized in Table 1.

Efficacy

The median PFS was 4.5 months (Topotecan 3.7 vs. Paclitaxel 5.5, HR = 0.34, 95% CI: 0.30-0.64, p<0.001) (Fig. 1), and the median OS was 11 months (Topotecan 9.5 vs. Paclitaxel 12.7, HR = 0.25, 95% CI: 0.20-0.45, p<0.001) (Fig. 2).

ORR was 10.2 % in the topotecan group and 20.3% in the weekly paclitaxel group (p=0.047). DCR was 15.5% in patients treated with topotecan and 28.8% in the paclitaxel group (p=0.033).

Details of comprehensive response results of second-line regimens are summarized in table 2.

Adverse Events

The topotecan and weekly paclitaxel treatment protocols had different toxicity profiles. There are no deaths due to adverse events. The most frequent adverse event was hematologic toxicity with 22.5% in the topotecan group and gastrointestinal toxicity with 11.8% in the paclitaxel group. Another common toxicity was neuropathy which occurred 10.1% in the weekly paclitaxel group and 1.4% in topotecan group. There was a statistically significant difference in

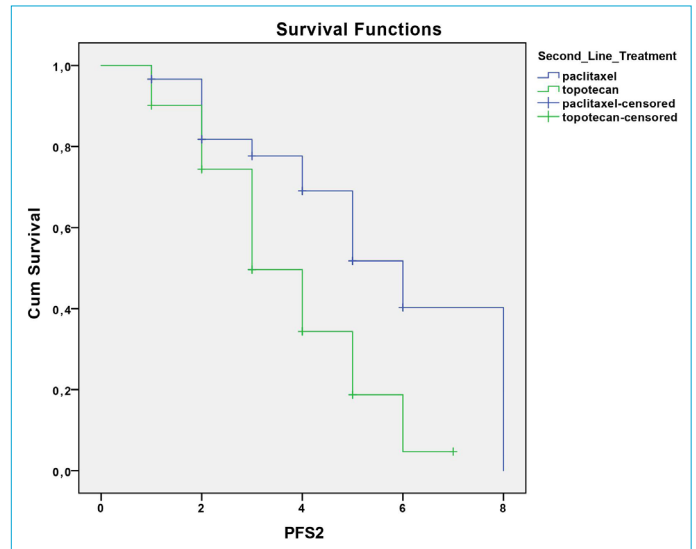


Figure 1. Kaplan–Meier curve of progression free survival between topotecan versus weekly paclitaxel.

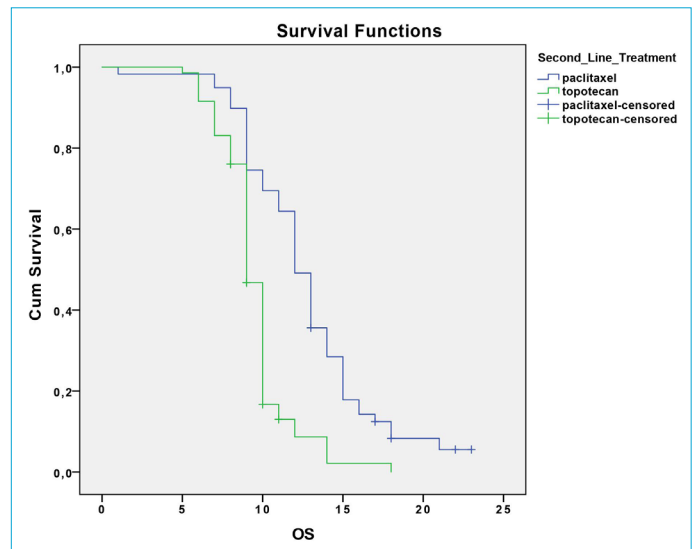


Figure 2. Kaplan–Meier curve of overall survival between topotecan versus weekly paclitaxel.

	Total (n:130)	Topotecan (n:71)	Paclitaxel group (n:59)	p
Gender				
Male	107 (82.3%)	64 (90.1%)	43 (72.8%)	0.010
Female	23 (17.7%)	7 (9.9%)	16 (27.2%)	
Median Age	59 (43-79)	60 (46-77)	61 (43-79)	0.914
BMI	24.9 (18.6-38.6)	25.4(18.6-38.6)	24.3(19.2-33.3)	0.112
ECOG				
0	54 (41.6%)	27 (38%)	27 (45.8%)	0.238
1	76 (58.4%)	44 (62%)	32 (54.2%)	
First Line Treatment				
Cisplatin plus Etoposide	105 (80.8%)	59 (83.2%)	45 (76.4%)	0.311
Carboplatin plus Etoposide	22 (16.9%)	11 (15.4%)	12 (20.3%)	
Chemo. plus Atezolizumab	3 (2.3%)	1 (1.4%)	2 (3.3%)	

Table 2. Efficacy of Topotecan and Paclitaxel

	Topotecan (n:71)	Paclitaxel (n:59)	p
Cycles (n)	4 (1-12)	3 (1-14)	0.067
DCR (CR+PR+SD)	11 (15.5%)	17 (28.8%)	0.033
ORR (CR+PR)	7 (10.2%)	12 (20.3%)	0.047
PFS Median (months, 95% CI)	3.7 (2.3-3.9)	5.5 (4.8-6.2)	<0.001
OS Median (months, 95% CI)	9.5 (8.9-10)	12.7 (11.1-13.1)	<0.001

the toxicity profile between the two groups; patients in the topotecan group had experienced more adverse events in all grades ($p=0.002$).

In the topotecan group, 20.9% of patients had grade 3-4 toxicity, 62% of patients needed dose reduction, and 12.1% of patients discontinued treatment. In the paclitaxel group 20.3% patients had grade 3-4 toxicity and 37.3% patients needed dose reduction. Additionally, 11.4% of patients discontinued treatment. There was no statistical difference between the two groups in grade 3-4 adverse events ($p=0.391$). But dose reduction rates were different, more dose reduction was needed in the topotecan group ($p=0.005$). The common treatment-related toxicities and grade 3-4 adverse events in the two groups are detailed in table 3.

Discussion

The present study showed prolonged survival parameters with the weekly paclitaxel compared with the topotecan, as second-line treatment of SCLC. The median OS was significantly better with 12.7 months in the weekly paclitaxel group versus 9.5 months in the topotecan group. Also, PFS was 5.5 months in the weekly paclitaxel compared to 3.7 months in the topotecan group with statistical significance. Patients' characteristic features were nearly homogenous; especially there was no difference between performance status ($p=0.238$). The distribution of the gender of the patients in each group was different; the number of the female patients was higher in the weekly paclitaxel group.

Table 3. Toxicities of Topotecan and Paclitaxel

	Topotecan (n)(%) All Grades	Paclitaxel (n)(%) All Grades	p
Hematological toxicity	16 (22.5)	2 (3.3)	0.002
Neuropathy	1 (1.4)	6 (10.1)	
Gastrointestinal Toxicity	4 (5.6)	7 (11.8)	
Other	2 (2.8)	1 (1.6)	
Grade 3-4	17 (20.9)	12 (20.3)	0.391
Dose reduction	44 (62)	22 (37.3)	0.005

Topotecan is the preferred regimen in the guidelines, but toxicity might be high, and many patients discontinue treatment. Due to common usage of weekly paclitaxel in other cancers, many centers choose this regimen although not preferred upfront in SCLC.

Topotecan is the preferred treatment regimen in the guidelines due to the phase 3 trials. Von Pawel J et al.^[12] compared cyclophosphamide, doxorubicin, and vincristine (CAV) versus topotecan in the second-line treatment of SCLC. This was a non-inferiority trial and topotecan and CAV had similar survival results with less toxicity in the topotecan arm. Oral topotecan was compared to the best supportive care (BSC) in another trial^[10] and improved survival rates were found. Due to the results of these studies, topotecan was accepted as the standard choice in the second-line treatment of SCLC. In the present study, DCR (15.5%) and ORR (10.2%) were consistent with the literature in the topotecan group. The Toxicity profile of the topotecan was also similar to the original studies. Hematological toxicity occurred in 22.5% and 20.9% had grade 3-4 adverse events. Additionally, similar rates of dose reductions were needed (62%). In the weekly paclitaxel group, patients experienced less toxicity in all grades with statistical significance ($p=0.002$). Especially the difference was evident in the hematological toxicity ($p=0.002$). Dose reduction rates were lower, and grade 3-4 adverse events were rarer in the weekly paclitaxel group, but only dose reduction rates were statistically significant between the two groups ($p=0.005$).

The efficacy of the weekly paclitaxel regimen in the second-line treatment of non-small cell lung cancer (NSCLC) was observed. Yasuda K. et al. had designed a study in the squamous cell subgroup of NSCLC patients. The DCR of the weekly paclitaxel in the second line was 31%.^[13] In another phase 2 trial, designed in patients diagnosed with NSCLC adenocarcinoma subgroup were treated with weekly paclitaxel in the second line and DCR was observed 36%.^[14] Weekly paclitaxel was investigated in the second line of SCLC treatment in a few studies. Yamamoto N. et al.^[15] evaluated the efficacy of weekly paclitaxel in the second-line of SCLC treatment and ORR was found 20%, DCR was observed 27.3% in the patients. Another taxane study in the second-line of SCLC treatment was performed by Smyth J.F. et al.^[16] and 34 patients received docetaxel. ORR and DCR were observed 20.5% and 25% respectively. Additionally, Smith E.F. et al.^[17] assessed the efficacy of paclitaxel (175 mg every 3 weeks) in the second-line treatment of SCLC. 25 patients were included and DCR and ORR were determined 48% and 28% respectively and four patients discontinued treatment. In the clinical routine, physicians usually accept that three-week 175 mgr. paclitaxel might be more toxic regimen and difficult to use especially compared to weekly

paclitaxel. Heavily pretreated SCLC patients are more fragile and for this reason weekly paclitaxel might be more appropriate for the second-line treatment of SCLC. In the present study, DCR and ORR results were determined similar, 28.8% and 20.3 respectively.

Few studies were conducted comparing topotecan and paclitaxel in the second-line treatment of SCLC. Zhao and colleagues^[18] evaluated the efficacy of second-line regimens in SCLC, four agents were included as irinotecan, topotecan, paclitaxel, and docetaxel. Firstly, receiving second-line treatment had resulted better compared to not receiving any second-line treatment. ORR resulted in 15.38% in the topotecan group and 21.43% in the paclitaxel group. The median OS was 184 days in the paclitaxel group and 154 days in the topotecan group. In another study,^[19] the platinum sensitive and resistant group were evaluated for the second-line treatment. In the platinum resistant patients, the paclitaxel and the topotecan regimen were compared and DCR was observed 25% in the paclitaxel group and 22.7% in the topotecan group. Toxicity and the dose reduction rates were better in the paclitaxel group but there was no statistical difference between two groups in both studies. The Low number of patients in the studies may have caused these results.

The present study has some limitations; firstly, it has been designed retrospectively with small sample size. Secondly, immunotherapies and one of the preferred regimens, lurbinectedin were not investigated. The difficulties of accessing lurbinectedin may end up with the physicians' chemotherapy preference in the second line of SCLC. Further investigations with higher numbers of patients are needed.

Conclusion

The weekly paclitaxel is an effective and tolerable regimen in the SCLC patients who have relapsed within 6 months to the first line platinum-based treatment. The present study had compared the preferred regimen topotecan to the weekly paclitaxel and the weekly paclitaxel had resulted in better survival and response rates. Also, dose reduction, and adverse event rates were better in the weekly paclitaxel. The weekly paclitaxel regimen that is currently an option for the second-line treatment of many tumors might also be considered for the platinum-resistant relapsed SCLC patients.

Disclosures

Ethics Committee Approval: The Institutional Review Board of Medeniyet University approved present retrospective cohort study (reference ID: 2021/0658).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – S.A.; Design – S.A.; Supervision – M.G.; Materials – D.T.O.; Data collection &/or processing – M.M.A., R.A.; Analysis and/or interpretation – D.T.O., O.D.; Literature search – A.G.A.; Writing – S.A.; Critical review – M.G.

References

1. Rudin CM, Brambilla E, Faivre-Finn C, Sage J. Small-cell lung cancer. *Nat Rev Dis Primers* 2021;7:3. [\[CrossRef\]](#)
2. Raso MG, Bota-Rabassedas N, Wistuba II. Pathology and classification of SCLC. *Cancers (Basel)* 2021;13:820. [\[CrossRef\]](#)
3. Ko J, Winslow MM, Sage J. Mechanisms of small cell lung cancer metastasis. *EMBO Mol Med* 2021;13:e13122. [\[CrossRef\]](#)
4. Wang S, Tang J, Sun T, Zheng X, Li J, Sun H, et al. Survival changes in patients with small cell lung cancer and disparities between different sexes, socioeconomic statuses and ages. *Sci Rep* 2017;7:1339. [\[CrossRef\]](#)
5. Paz-Ares L, Dvorkin M, Chen Y, Reinmuth N, Hotta K, Trukhin D, et al; CASPIAN investigators. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. *Lancet* 2019;394:1929–39. [\[CrossRef\]](#)
6. Liu SV, Reck M, Mansfield AS, Mok T, Scherpereel A, Reinmuth N, et al. Updated overall survival and PD-L1 subgroup analysis of patients with extensive-stage small-cell lung cancer treated with atezolizumab, carboplatin, and etoposide (IMpower133). *J Clin Oncol* 2021;39:619–30.
7. Neal JW, Gubens MA, Wakelee HA. Current management of small cell lung cancer. *Clin Chest Med* 2011;32:853–63.
8. Jett JR, Schild SE, Kesler KA, Kalemkerian GP. Treatment of small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2013;14:e400S–e19S.
9. Horn L, Mansfield AS, Szczesna A, Havel L, Krzakowski M, Hochmair MJ, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. *N Engl J Med* 2018;379:2220–9. [\[CrossRef\]](#)
10. O'Brien ME, Ciuleanu TE, Tsekov H, Shparyk Y, Cucevia B, Juhász G, et al. Phase III trial comparing supportive care alone with supportive care with oral topotecan in patients with relapsed small-cell lung cancer. *J Clin Oncol* 2006;24:5441–7.
11. Trigo J, Subbiah V, Besse B, Moreno V, Lopez R, Sala MA, et al. Lurbinectedin as second-line treatment for patients with small-cell lung cancer: a single-arm, open-label, phase 2 basket trial. *Lancet Oncol* 2020;21:645–54. [\[CrossRef\]](#)
12. von Pawel J, Schiller JH, Shepherd FA, Fields SZ, Kleisbauer JP, Chrysson NG, et al. Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small-cell lung cancer. *J Clin Oncol* 1999;17:658–67. [\[CrossRef\]](#)
13. Yasuda K, Igishi T, Kawasaki Y, Kato K, Matsumoto S, Katayama

- S, et al. Phase II study of weekly paclitaxel in patients with non-small cell lung cancer who have failed previous treatments. *Oncology* 2004;66:347–52. [\[CrossRef\]](#)
14. Ceresoli GL, Gregorc V, Cordio S, Bencardino KB, Schipani S, Cozzarini C, et al. Phase II study of weekly paclitaxel as second-line therapy in patients with advanced non-small cell lung cancer. *Lung Cancer* 2004;44:231–9. [\[CrossRef\]](#)
 15. Yamamoto N, Tsurutani J, Yoshimura N, Asai G, Moriyama A, Nakagawa K, et al. Phase II study of weekly paclitaxel for relapsed and refractory small cell lung cancer. *Anticancer Res* 2006;26:777–81.
 16. Smyth JF, Smith IE, Sessa C, Schoffski P, Wanders J, Franklin H, et al. Activity of docetaxel (Taxotere) in small cell lung cancer. The Early Clinical Trials Group of the EORTC. *Eur J Cancer* 1994;30A:1058–60. [\[CrossRef\]](#)
 17. Smit EF, Fokkema E, Biesma B, Groen HJ, Snoek W, Postmus PE. A phase II study of paclitaxel in heavily pretreated patients with small-cell lung cancer. *Br J Cancer* 1998;77:347–51.
 18. Zhao Y, Wan B, Zhang T, Xu Y, Liu H, Lv T, et al. Irinotecan, topotecan, paclitaxel or docetaxel for second-line treatment of small cell lung cancer: a single-center retrospective study of efficiency comparison and prognosis analysis. *Transl Lung Cancer Res* 2019;8:829–37. [\[CrossRef\]](#)
 19. Li Z, Liu X, Li J, Gao H, Tang C, Li X, et al. comparison of efficacy and safety of different therapeutic regimens as second-line treatment for small cell lung cancer. *Zhongguo Fei Ai Za Zhi* 2015;18:280–8.