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Research Article

Third-line Treatment is Associated with Prolonged Survival in Patients with Extensive-Stage Small Cell Lung Cancer: A Single Center Experience

Mustafa Karaagac, Mehmet Artac

Department of Medical Oncology, Necmettin Erbakan University Meram Faculty of Medicine, Konya, Turkey

Abstract

Objectives: The efficacy of third-line (3L) chemotherapy is controversial in patients with extensive-stage small cell lung cancer. In this study, we aimed to assess the effectiveness of 3L chemotherapy in our cohort.

Methods: This was a single-center, retrospective, cross-sectional, and cohort study. A total of 55 patients were evaluated.

Results: Forty-two patients (76.4%) received 3L treatment, whereas 13 patients (23.6%) who required therapy because of progressive disease did not receive 3L treatment. The overall response rate was 7.1%. The median progression-free survival (PFS) was 2.82 months. The median overall survival (OS) of all patients, patients who received 3L treatment, and patients who did not receive 3L treatment were 19.97 months, 21.63 months and 14.62 months, respectively. Good performance status was detected as a significant univariate parameter for median PFS (p=0.048), but was not meet the statistical significance criteria in multivariate analysis. Receiving 3L treatment and good performance status were the significant parameters for OS both in univariate (p=0.019 and p=0.045) and multivariate analysis (p=0.022 and p=0.048).

Conclusion: We demonstrated that receiving 3L treatment and good performance status were associated with increased OS. In addition, we revealed that good performance status might be associated with prolonged PFS achieved by 3L treatment.

Keywords: Extensive, third-line chemotherapy, small cell lung cancer, survival

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Lung cancer is the most common and fatal cancer, and is divided into two main subtypes based on tumor histology as non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC).[1] SCLC subtype, which accounts for approximately 12% of lung cancer cases, is less common than NSCLC subtypes but is associated with a more aggressive course and short survival despite treatment.[2,3] Although immunotherapy drugs, in addition to chemotherapy, have started to be used in SCLC treatment, conventional chemotherapy is still the mainstay of treatment.[4] The majority of patients with extensive-stage SCLC (ES-SCLC) can only receive two lines of chemotherapy. Although it shows modest efficacy, second-line chemotherapy is usually recommended for the progressive disease.[5] When disease progression is detected despite second-line therapy, further treatments may be considered in patients with good performance status, but the efficacy of third-line (3L) chemotherapy is controversial.[6]

Address for correspondence: Mustafa Karaagac, MD. Necmettin Erbakan Universitesi Meram Tip Fakultesi, Tibbi Onkoloji Anabilim Dali, Konya, Turkey
Phone: +90 505 745 58 12 **E-mail:** mustafakaraagac55@hotmail.com

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In this study, we aimed to assess the effectiveness of 3L chemotherapy on survival, and to identify the parameters that affect the outcomes of 3L chemotherapy in patients with SCLC, compared to best supportive care.

Methods

This was a single-center, retrospective, cross-sectional, and cohort study. Age ≥18, having histologically or cytologically proven ES-SCLC, having progressive disease after two lines of chemotherapy, and receiving the 3L treatment were the inclusion criteria. The files of all eligible patients who treated and followed-up in our cancer center between July 2009 and July 2019 were evaluated. All of the data were collected and recorded by one medical oncologist.

The staging of all patients in this study was determined according to the 7th edition of the American Joint Committee on Cancer staging system. The response evaluation of the patients was done according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Patients who achieved a complete response (CR), partial response (PR), and stable disease (SD) in accordance with RECIST were defined as 'responders'. In contrast, patients with progressive disease (PD) were identified as 'non-responders'. The overall response rate (ORR) was defined as the responders, including only CR or PR. The Eastern Cooperative Oncology Group-Performance Score (ECOG-PS) was used to determine the performance status of the patients. ECOG-PS ≤1 was named as 'good performance', whereas ECOG-PS ≥2 was called as 'poor performance'.

Survival definitions consisted of progression-free survival (PFS) and overall survival (OS). PFS was defined as PFS-1 and PFS-2. PFS-1 was calculated as the time from the beginning of the first-line treatment to the date of first disease progression after the second-line treatment. PFS-2 was calculated as the time from the beginning of the 3L treatment to the date of first disease progression despite the 3L treatment or death from any cause in the period of 3L treatment. And, OS was calculated as the time from the beginning of the first-line treatment to the date of death or last visit. All patients underwent PFS-1 and OS analysis. Furthermore, PFS-2 analysis was performed only on patients who received 3L treatment.

Statistical analysis was performed by using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA). A p-value <0.05 was required for statistical significance. Primary statistical analysis has included descriptive statistics of the patients. Descriptive statistics were calculated as proportions and medians. The Kaplan–Meier method was used for survival analysis. Log-Rank analysis was performed to compare the different subgroups. Univariate and multivariate Cox regression analyses were used to identify independent variables.

Results

A total of 55 patients were assessed in this study. There were 52 males (94.5%) and three females (5.5%). The median age at the time of diagnosis was 59.3 years (range; 30-79 years). Forty-two patients (76.4%) received 3L treatment because of progressive disease, whereas 13 patients (23.6%) who required therapy did not receive 3L treatment despite the progressive disease. Of the 42 patients receiving 3L treatment, 20 (47.6%) received single-agent chemotherapy regimens, and the remaining 22 patients (52.4%) received combination therapies. The most commonly used single-agent treatment was monotherapy topotecan, while the most commonly used combination treatment was including cyclophosphamide, adriamycin, and vincristine (CAVi regimen). Disease progression was detected in all patients despite 3L treatment. Table 1 shows the details of demographic and clinical parameters of patients, and table 2 desciribes the details of chemotherapy regimens administered to the patients.

The percentage of responder patients to 3L treatment was 23.8%, but the ORR was 7.1%. Because, most of the responder patients had SD. Table 2 also shows the details of the responses obtained by 3L treatment.

The median PFS-1 values of all patients, the patients who received 3L treatment, and the patients who did not receive 3L treatment were 13.07 months (range; 4.07-37.42), 13.79 months (range; 4.07-37.42), and 10.77 months (range; 5.59-22.47), respectively. Furthermore, the median PFS-2 of the patients who received 3L treatment was 2.82 months (range; 0.30-10.74). The median OS values of all patients, the patients who received 3L treatment, and the patients who did not receive 3L treatment were 19.97 months (range; 6.37-82.40), 21.63 months (range; 8.51-82.40), and 14.62 months (6.37-41.63), respectively. Please see table 2 for the survival outcomes of 3L treatment.

No significant parameter was found in the univariate analysis of all patients for PFS-1. Good performance status at the beginning of 3L treatment was detected as the univariate parameter significantly affecting the median PFS-2 (p=0.048, 95% confidence interval (95% CI): 1.478-2.201). However, good performance status at the beginning of 3L treatment did not meet the statistical significance criteria in the multivariate analysis (p=0.053, Wald: 3.746, 95% CI: 0.255-1.009).

In the univariate analysis of all patients for OS, receiving the 3L treatment and good performance status at the beginning of 3L treatment were the significant parameters

Table 1. The details of demographic and clinical parameters of patients

	Patients not-receiving 3L treatment		Patients receiving 3L treatment		All patients	
	n=13	%	n=42	%	n=55	%
Age						
Median	58.7		56.8		57.3	
Minimum	44.0		30.0		30.0	
Maximum	67.0		79.0		79.0	
Gender						
Female	0	0	3	7.1	3	5.5
Male	13	100	39	92.9	52	94.5
Smoking						
Never	0	0	2	4.8	2	3.6
Ex smoker	1	7.7	4	9.5	5	9.1
Active	12	92.3	36	85.7	48	87.3
Comorbidity						
Present	6	46.2	13	31	19	34.5
Absent	7	53.8	29	69	36	65.5
Initial stage						
Stage-3	1	7.7	3	7.1	4	7.3
Stage-4	12	92.3	39	92.9	51	92.7
Sites of metastasis						
Only lung	1	7.7	0	0	1	1.8
Only bone	1	7.7	3	7.1	4	7.3
Only brain	1	7.7	5	11.9	6	10.9
Only surrenal	0	0	1	2.4	1	1.8
Only liver	1	7.7	1	2.4	2	3.7
Only servical LN	0	0	1	2.4	1	1.8
Only mediastinal LN	1	7.7	3	7.1	4	7.3
Only abdominal LN	0	0	1	2.4	1	1.8
Multiple	8	61.5	27	64.3	35	63.6
Performance status (at daignosis)						
Good performance	12	92.3	36	85.7	48	87.3
Poor performance	1	7.7	6	14.3	7	12.7
Performance status (at the beginning of 3L treatment)						
Good performance	1	7.7	14	33.3	15	27.3
Poor performance	12	92.3	28	66.7	40	72.7
Final status						
Exitus	13	100	41	97.6	54	98.2
Alive	0	0	1	2.4	1	1.8

3L: third-line; n:number of patients; LN: lymph nodes.

(p=0.019, 95% CI: 15.682-24.794, and p=0.045, 95% CI: 19.665-22.651, respectively). Moreover, receiving the 3L treatment and good performance status at the beginning of 3L treatment retained their significance in the multivariate analysis (p=0.022, Wald: 5.236, 95% CI: 0.251-0.899, and p=0.048, Wald: 3.904, 95% CI: 1.005-3.525, respectively). Figure 1 and figure 2 show the Kaplan-Meier curves of OS analysis.

In addition, receiving 3L treatment as a single agent or combination was not statistically significant.

Discussion

In this study, we evaluated the patients with ES-SCLC who received at least two lines treatment and demonstrated that receiving the 3L treatment and good performance status at the beginning of 3L treatment were associated

Table 2. The details of chemotherapy regimens administered to the patients, responses obtained by third-line treatment, and survival outcomes of third-line treatment

	Patients not-receiving 3L treatment		Patients receiving 3L treatment		All patients	
	n=13	%	n=42	%	n=55	%
3L chemotherapy regimens						
Single-agent regimens			20	47.6		
Topotecan			10	23.8		
Paclitaxel			6	14.3		
İrinotecan			4	9.5		
Combination regimens			22	53.4		
CAVi			8	19		
Cisplatin+irinotecan			6	14.3		
Cyclophosphamide+etoposide			4	9.5		
Carboplatin+paclitaxel			3	7.1		
Carboplatin+ etoposide			1	2.4		
Cycles of 3L chemotherapy *						
Median			3.02			
Minimum			1.00			
Maximum			6.00			
Responses to 3L chemotherapy						
Responder			10	23.8		
CR			0	0		
PR			3	**7.1		
SD			7	16.7		
Non-responder						
PD			32	76.2		
PFS-1						
Median	10.77		13.79		13.07	
Minimum	5.59		4.07		4.07	
Maximum	22.47		37.42		37.42	
PFS-2						
Median			2.82			
Minimum			0.30			
Maximum			10.74			
OS						
Median	14.62		21.63		19.97	
Minimum	6.37		8.51		6.37	
Maximum	41.63		82.40		82.40	

3L: third-line; n: number of patients; CAVi: cyclophosphamide+adriamycine+vincristine; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; PFS: progression-free survival; OS: overall survival; *: 1 cycle refers to all chemotherapy treatments every 21 days or for 21 days; **:the overall response rate.

with increased OS. Moreover, we revealed that good performance status at the beginning of 3L treatment might be associated with prolonged PFS achieved by 3L treatment.

SCLC is an aggressive disease that is associated with limited treatment options and short survival despite therapy. Patients with ES-SCLC are usually responder to first-line platinum-based treatment.[7] However, the response is unsustainable, and further therapy is needed due to disease progression in the first year of almost all patients.[8] Nevertheless, it was showed that the majority of patients with ES-SCLC could only receive two lines of treatment, and despite therapy, the majority of patients die within one year.[6,9] Although it was revealed that the 3L and beyond lines treatments for ES-SCLC might be useful to improve survival, there is not an exact consensus on this issue.[6,9,10] Moreover, for the patients who progress on first-line and second-line treatments, clinical trial enrollment is the preferred treatment option under the National Comprehensive Cancer Network (NCCN) SCLC guidelines.[11] However, as in many regions of our country, it is almost impossible to access

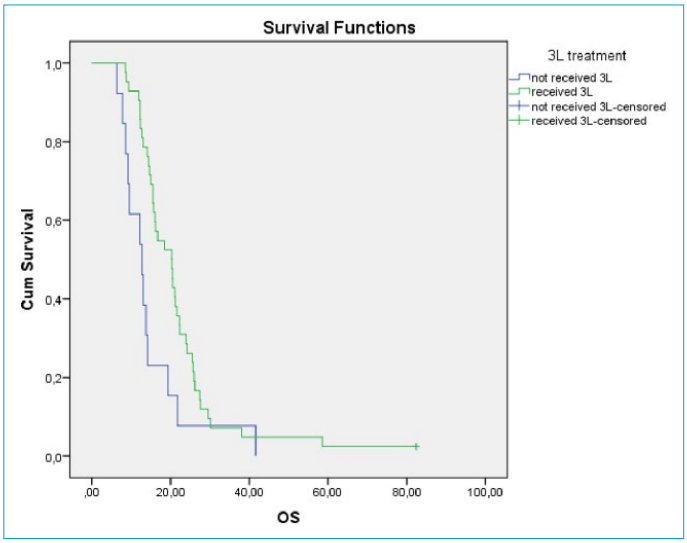

Figure 1. The Kaplan-Meier curve of OS analysis: receiving 3L treatment. In the univariate analysis of all patients for OS, receiving 3L treatment was a significant parameter (p=0.019, 95% CI: 15.682-24.794). And, receiving 3L treatment retained its significance in the multivariate analysis (p=0.022, Wald: 5.236, 95% CI: 0.251-0.899).

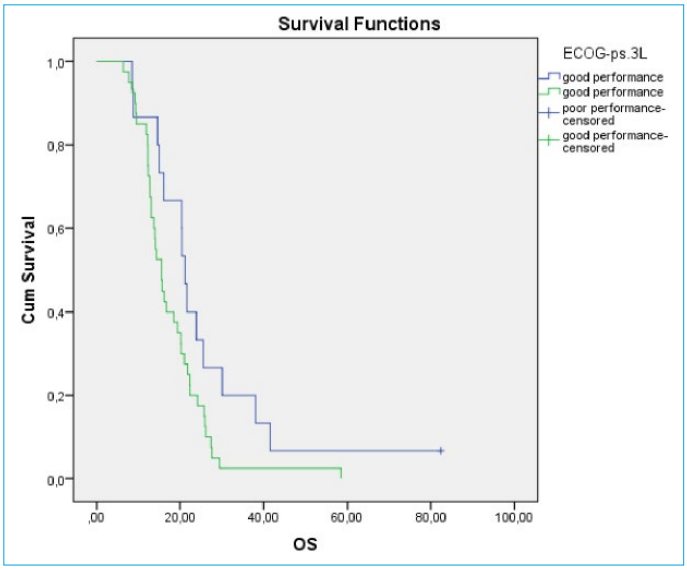

Figure 2. The Kaplan-Meier curve of OS analysis: performance status. In the univariate analysis of all patients for OS, good performance status at the beginning of 3L treatment was a significant parameter (p=0.045, 95% CI: 19.665-22.651). And, good performance status at the beginning of 3L treatment retained its significance in the multivariate analysis (p=0.048, Wald: 3.904, 95% CI: 1.005-3.525).

clinical trials in most parts of the world.

Although the information on the efficacy of 3L chemotherapy in patients with ES-SCLC is mostly based on earlier studies, it was revealed that current treatments utilized in the 3L and beyond 3L provide a limited increase in survival. Besides, patients left untreated and placed on supportive care after front-line treatments mostly live less than one month.[12] Furthermore, in this study, we demonstrated that receiving 3L treatment was associated with a statistically significant OS advantage. Moreover, we showed that median PFS in 3L systemic therapy was 2.82 months. Also, it was confirmed in our study that good performance status is associated with prolonged survival. This study is critical since it provides current real-life data on treatment approaches and treatment responses. The current study reveals one of the real-world studies and, the results we have shown here coincide with the data from the two precious studies conducted recently.[12,13]

Considering that the majority of the patients received only two lines treatments in most of the world and that most of the cancer centers did not use the 3L treatment, our results showed that it is absolutely necessary to keep in mind the recommendation of 3L treatment for tolerable patients. In addition, we should be aware that combination chemotherapy does not show any survival advantage in the 3L treatment, as demonstrated in this study and shown in the literature.[14]

Nevertheless, in this study, the knowledge about the adverse effects of the 3L treatment was not presented. Because the data on adverse effects that the clinician would determine by physical examination had not been recorded adequately in the files of our cohort, so the assessment would not be sufficient and reliable. Therefore, we did not analyze data on the adverse effects of the 3L treatment in order to avoid any bias.

The major limitations of this study are that the retrospective design, the low number of patients, and the lack of data on adverse effects due to the treatments.

Conclusion

Although the current chemotherapy regimens in the treatment of ES-SCLC are not curative, the results of our study were demonstrated that the available therapeutic options must be offered for the patients with ES-SCLC who failed after two lines treatment. However, when making treatment decisions, it should take into account several conditions such as comorbidity, performance, the disease-free interval from previous treatment, and toxicity.

Disclosures

Ethics Committee Approval: The study was performed according to the Declaration of Helsinki and approved by the Local Ethics Committee (Ethics Committee approval number: 2019/2167). Patient informed consent was not required because this was a retrospective cross-sectional file scanning study.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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