

The Clinical Features and Treatment Responses of Small Cell Lung Cancer Patients: A Single-Center Experience

Küçük Hücreli Akciğer Kanserli Hastalarımızın Klinik Özellikleri ve Tedavi Yanıtları; Tek Merkez Deneyimi

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INTRODUCTION

Lung cancer is the most common and fatal cancer, regardless of gender (1). Small cell lung cancer (SCLC) subtype, which accounts for approximately 15% of lung cancer cases, is less common than non-small cell subtypes but is associated with a more aggressive course and short survival (2). Although immunotherapy drugs, in addition to chemotherapy

(CT), have started to be used in SCLC treatment in developed countries, conventional CT is still the mainstay of treatment in most of the world (3).

However, the majority of information on CT, as well as information on demographic data of patients, is based on studies from several decades ago. Besides, clinical observations suggest that current treatment approaches, patient adherence to treatment, and

Öz

Amaç: Küçük hücreli akciğer kanseri (KHAK) agresif gidişatla ve kısa sağkalım süresi ile ilişkilidir. KHAK tedavisinin esasını konvansiyonel kemoterapi oluşturmaktadır. Bu çalışmamızda, KHAK' li hastaların güncel demografik ve klinik özelliklerinin tespit edilmesi ve uygulanan tedavilere alınan yanıtlarının belirlenmesi amaçlandı.

Hastalar ve Yöntem: Bu bir retrospektif, kesitsel, kohort çalışmasıdır. Tedavi sonucunda radyolojik olarak tam yanıt (CR), kısmi yanıt (PR) ve stabil yanıt (SD) elde edilen hastalar "yanıtlı" olarak değerlendirilirken, hastalık ilerlemesi (PD) saptanan hastalar "yanıtsız" olarak değerlendirildi. Sağkalım tanımlamaları; tüm sağkalım süresinden (TOS) ve metastaz gelişiminden sonraki sağkalım süresinden (MOS) oluştu. TOS ile, KHAK' nin ilk saptandığı andan ölüme/sonvizite kadar geçen süre, MOS ile metastazın saptandığı andan ölüme/sonvizite kadar geçen süre ifade edildi.

Bulgular: Çalışmada 161 hastanın verileri incelendi. 1. seri KT, 2. seri KT ve 3. seri KT ile elde edilen yanıt oranları sırasıyla %72.2, %43.3 ve %40.4 olarak belirlendi. Medyan TOS 15.7 ay (0.03-106.97), medyan MOS ise 13.79 (0.03-79.54) olarak hesaplandı. Hastaların medyan TOS değerini etkileyen univariate parametreler; kötü performans skoru, tanıda metastatik hastalık varlığı, tedaviyi reddetmek olarak belirlendi.

Sonuç: Tedaviyi tolere edebilecek performansa sahip hastaların, hastalığın hangi sürecinde olursa olsun, tedavi çemberinde yer almalarının sağkalım avantajı ile neticelendiği gösterildi. .

Anahtar Kelimeler: Akciğer kanseri, küçük hücreli, kemoterapi, sağkalım

Abstract

Aim: Small cell lung cancer (SCLC) is associated with an aggressive course and short survival. Conventional chemotherapy (CT) is the mainstay of SCLC treatment. In this study, we aimed to determine the current demographic and clinical characteristics of patients with SCLC and to determine their responses to the treatments.

Patients and Methods: This was a retrospective, cross-sectional, cohort study. Definitions of survival were overall survival (TOS) and survival after metastasis (MOS). TOS was calculated as the time from the diagnosis to the date of death or last visit. MOS was calculated as the time from the diagnosis of metastasis to the date of death or last visit.

Results: The data of 161 patients were analyzed. Response rates obtained with 1st line CT, 2nd line CT, and 3rd line CT were 72.2%, 43.3%, and 40.4%, respectively. The median TOS and median MOS were calculated as 15.7 months (0.03-106.97) and 13.79 months (0.03-79.54), respectively. The presence of metastatic disease at the time of diagnosis and refusal of treatment were statistically significant parameters affecting the median TOS.

Conclusions: It was shown that the patients who received and were able to tolerate the treatment had obtained a survival advantage, regardless of the disease phase.

Key words: Lung cancer, small cell, chemotherapy, survival

treatment responses differ from previous decades. In this study, we aimed to determine the current demographic and clinical characteristics of our cohort and to determine their responses to the treatments.

PATIENTS AND METHODS

This was a single-center, retrospective, cross-sectional, and cohort study. The study was performed according to the Declaration of Helsinki and approved by the Local Ethics Committee of the university (Local Ethics Committee approval number: 2019/2167). Since this was a retrospective file screening study, informed consent was not required.

In this study, the files of all patients with SCLC who treated and followed-up in our cancer center between July 1, 2009, and July 1, 2019, were evaluated without exception. 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 Eastern Cooperative Oncology Group-Performance Score (ECOG-PS) was used to determine the performance status of the patients. ECOG-PS ≤ 2 was named as 'good performance', whereas ECOG-PS ≥ 3 was called as 'poor performance'.

Survival definitions consisted of the overall survival (TOS) and survival after metastasis (MOS). TOS was calculated as the time from the diagnosis to the date of death or last visit. And, MOS was calculated as the time from the diagnosis of metastasis to the date of death or last visit. All patients underwent TOS and MOS analysis.

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 161 patients were assessed in this study. There were 151 males (93.8%) and ten females (6.2%). The median age at the time of diagnosis was 60.8 years (range; 30-86 years). Eighteen patients (11.2%) received primary CT and radiotherapy because of limited-stage. The number of metastatic patients at the time of diagnosis was 142 (88.2%). Metastases were developed in an additional 12 patients, but seven patients never had a metastasis. Of the 154 metastatic patients, 104 had more than one organ or system metastasis. The details of the demographic and clinical parameters of patients are shown in Table 1.

The median TOS and median MOS were calculated as 15.7 months (0.03-106.97) and 13.79 months (0.03-79.54), respectively. Although they were metastatic, ten patients had never received first-line CT, and the median MOS was 1.88 months and 14.62 months, respectively, in those who did not receive CT and received CT. Twenty-one (18.9%) of the 111 patients who needed second-line treatment did not receive CT, and the median MOS was 8.39 months and 18.45 months, respectively, in those who did not receive CT and received CT. Eighteen of the 65 patients (27.7%) who required the third-line treatment did not receive CT, and the median MOS was found to be 15.36 months and 23.86 months, respectively in those who did not receive CT and received CT. 31 patients (19.3%) received the fourth-line treatment, and six patients (3.7%) received the fifth-line treatment.

Platinum-based CT regimens were applied in the first-line setting of treatment in almost all patients with extensive-stage. Platinum-free treatment regimens were preferred for subsequent lines of treatment. The details of the chemotherapies administered to the patients are described in table-2.

Although 72.2% of the patients who were treated for extensive-stage disease responded to the first-line treatment, the response rates to the treatments applied in the subsequent lines remained below 50%. The details of the treatment responses of the patients are shown in table-3.

Poor performance status, presence of metastatic disease at the time of diagnosis, and refusal of treatment were detected as the univariate parameters affecting the median TOS. In multivariate analysis, the presence of metastatic disease at the time of diagnosis and refusal of treatment continued to be statistically significant. The details of the univariate parameters

Table 1. The demographic and clinical parameters of patients

				n=161	%
Age at diagnosis					
minimum	30,00				
maximum	86,00				
median	60,80				
Gender					
female				10	6,2
male				151	93,8
Smoking					
never				10	6,2
ex-smoker				13	8,1
active				138	85,7
Performance status					
ECOG-PS:1				133	82,6
ECOG-PS:2				21	13,0
ECOG-PS:3				5	3,1
ECOG-PS:4				2	1,2
Stage					
stage-1				1	,6
stage -2				3	1,9
stage -3				15	9,3
stage -4				142	88,2
Sites of metastasis					
more than one field				104	64,6
bone				58	36,0
liver				47	29,2
brain				37	23,0
surrenal				29	18,0
Number of CT cycles					
	1st line	2nd line	3rd line		
minimum	1,00	1,00	1,00		
maximum	12,00	13,00	12,00		
median	4,97	3,84	4,15		
Final status					
death				139	86,3
alive				22	13,7

ECOG-PS: Eastern Cooperative Oncology Group-Performance Score, CT: Chemotherapy

affecting the median TOS are given in table-4. Poor performance status and refusal of treatment were detected as the univariate parameters affecting the median MOS. Moreover, these two parameters remained statistically significant in multivariate analysis. Please refer to table-5 for details.

DISCUSSION

To the best of our knowledge, this is the only study on the clinical data of patients with SCLC in our country in the last decade. This is a critical study since it provides data on current treatment approaches, patient compliance, and treatment responses.

In this study, we demonstrated that the majority of patients with SCLC had a history of smoking, mostly male patients, a significant portion of the disease at

the time of diagnosis was detected as an extensive-stage, and most of the patients had metastases at more than one organ system. Also, we showed that the majority of patients responded to the first-line of treatment, but the response was unsustainable, and subsequent response rates were reduced. Moreover, we revealed that poor performance status and refusal of treatment were associated with decreased survival.

While SCLC constituted approximately 17% of all lung cancers in the 1980s, this rate declined to approximately 12% in the early 2000s. The main reason for this is the gradual decrease in smoking. However, smoking is still known as the most crucial factor in the etiology of this cancer (4). Almost all of our patients had a history of smoking. However, in contrast to the recent decline in the consumption of

Table 2. The chemotherapy regimens and distribution of patients

	n	in group, %	in all patients, %
1st line CT	154	100	95,7
Not received	10	6,5	6,2
Received	144	93,5	89,4
cisplatin+etoposide	124	86,1	77,0
carboplatin+etoposide	18	12,5	11,2
monotherapy carboplatin	1	,7	,6
orally etoposide+cyclophosphamide	1	,7	,6
2nd line CT	111	100,0	68,9
Not received	21	18,9	13,0
Received	90	81,1	55,9
cisplatin+etoposide	2	1,8	1,2
cisplatin+vinorelbine	1	,9	,6
capecitabine+temozolomide	1	,9	,6
carboplatin+paclitaxel	1	,9	,6
carboplatin+etoposide	3	2,7	1,9
monoterapi karboplatin	1	,9	,6
cisplatin+irinotecan	4	0,36	2,5
CAVi	34	30,6	21,1
monotherapy topotecan	21	18,9	13,0
orally etoposide+cyclophosphamide	14	12,6	8,7
monotherapy etoposide	3	2,7	1,9
monotherapy irinotecan	5	4,5	3,1
3rd line CT	65	100,0	40,4
Not received	18	27,7	11,2
Received	47	72,3	29,2
monotherapy paclitaxel	6	9,2	3,7
monotherapy cyclophosphamide	1	1,5	,6
carboplatin+paclitaxel	4	6,2	2,5
carboplatin+etoposide	1	1,5	,6
cisplatin+irinotecan	6	9,2	3,7
CAVi	9	13,8	5,6
monotherapy topotecan	8	12,3	5,0
orally etoposide+cyclophosphamide	7	10,8	4,3
monotherapy etoposide	1	1,5	,6
monotherapy irinotecan	4	6,2	2,5

CAVi: Cyclophosphamide+Adriamycin+Vincristine, CT: Chemotherapy

cigarettes in the general population, its use among women, especially in developed societies has been increasing recently, leading to an increased incidence of SCLC in younger women (5). Nevertheless, the fact that almost all of our patients consisted of men may be due to the older average age of our cohort and the low proportion of women who smoke in our society (6).

It has been shown that approximately two-thirds of patients with SCLC have an extensive-stage disease at the first diagnosis, and metastases are detected in multiple areas at the time of diagnosis. This is related to decreased survival (7). However, as in limited-stage disease, it is reported that better treatment responses and survival can be achieved when detected as oligometastatic disease, even if it is an extensive-

Table 3. The responses to chemotherapy

	Radiological CR,%	Radiological PR,%	Radiological SD,%	Responder,% (CR/PR/SD)	Non-responder, % (PD)
1st line CT	9,0	37,5	25,7	72,2	27,8
2nd line CT	0	12,2	31,1	43,3	56,7
3rd line CT	0	10,6	29,8	40,4	59,6

CT: Chemotherapy, CR: Complete response, PR: Partial response, SD: Stable disease, PD: Progressive disease

Table 4. The parameters affecting median overall survival

Significant findings in the univariate regression analysis			
	P value	95% CI	
poor performance status	0.019	10.33-14.36	
metastatic disease at the time of diagnosis	0.001	9.01-12.40	
refusal of 1st line treatment	0.001	0.00-0.96	
refusal of 2nd line treatment	0.001	6.98-8.85	
refusal of 3rd line treatment	0.003	6.98-18.05	
Significant findings in the multivariate regression analysis			
	Wald	P value	95% CI
metastatic disease at the time of diagnosis	13.103	0.004	1.54-4.25
refusal of 1st line treatment	26.335	<0.001	2.92-11.03
refusal of 2nd line treatment	13.338	<0.001	1.54-4.17
refusal of 3rd line treatment	8.168	0.004	1.29-3.95

CI: Confidence Interval

stage disease (8). Nevertheless, as in the literature, the majority of our patients consisted of extensive-stage and poly-metastatic patients.

A partial improvement in the treatment results of limited-stage SCLC was achieved in the last four decades with CT, co-administered radiotherapy, and additional prophylactic cranial irradiation (9,10). However, the prognosis of SCLC is still worse. Patients with SCLC are usually responder to platinum-based treatment in the first-line setting, with a response rate of approximately 60-70% (11). This response rate was similarly demonstrated in our study. However, the response is not sustainable, and there is almost always a recurrence in the first two years. Besides, as a result of systemic metastases, the general health status of the patients gradually deteriorates (12,13). Ultimately, despite treatment, the majority of patients die within one year (14). The findings herein we demonstrated are consistent with this issue. Our patients also well-responded to the first-line treatment,

and as expected, this response was not sustainable. However, survival was approximately 20% longer in our patients than in the literature.

The majority of patients with extensive-stage SCLC can only receive two lines of treatment (15). Although it has been shown that maintenance/consolidation CT may be useful to improve survival, the third-line and beyond lines treatments for SCLC are controversial (15,16). Only one-quarter of our patients were able to receive the third-line of treatment. However, it is essential that the response rates to the third-line treatment of our cohort were excellent and that receiving third-line treatment led to a statistically significant increase in survival. Also, it is highly probable that approximately 20% longer median survival in our patients was due to this condition. In our opinion, these results are especially important for countries with a meager health budget. Because, when the current literature on the treatment of SCLC is examined, it is seen that the data related to

Table 5. The parameters affecting median survival after metastasis

Significant findings in the univariate regression analysis			
	P value	95% CI	
poor performance status	0.039	8.88-12.54	
refusal of 1st line treatment	<0.001	0.00-0.97	
refusal of 2nd line treatment	<0.001	6.95-8.22	
refusal of 3rd line treatment	0.007	6.98-18.05	
Significant findings in the multivariate regression analysis			
	Wald	P value	95% CI
poor performance status	9.462	0.051	1.32-4.48
refusal of 1st line treatment	43.131	<0.001	5.01-19.70
refusal of 2nd line treatment	27.367	<0.001	2.38-6.75
refusal of 3rd line treatment	7.026	0.008	0.27-0.82

CI: Confidence Interval

traditional CT applications are replacing with the data of economically expensive immunotherapy regimens (17,18). However, despite all these high costs, the median survival is not far beyond the results that we presented here. Considering that the majority of the patients received only two line treatments in most of the world and that most of the cancer centers did not use the third-line treatments, our results showed that it is absolutely necessary to keep in mind the recommendation of third-line treatment for tolerable patients.

As in patients with non-small cell lung cancer, poor performance status is a factor that adversely affects survival in patients with SCLC (19,20). It was confirmed in our study that poor performance status is an adverse prognostic factor. The limitations of this study are that the retrospective design, the lack of randomization, relatively low number of patients, and the lack of data on adverse effects due to the treatments.

CONCLUSIONS

In this study, it was confirmed that early diagnosis of SCLC is associated with a survival advantage. Although the current CT regimens in the treatment of SCLC are not curative, the results of our study were demonstrated that the patients who received and were able to tolerate the treatment had obtained a survival advantage, regardless of the disease phase. Further prospective studies with a larger number of patients are needed to validate these results.

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