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Predictive Factors of Complete Tumor Response to First Line Chemotherapy in Patients with Extensive-stage Small Cell Lung Cancer

Yaygın Evreli Küçük Hücreli Akciğer Kanseri Tanılı Hastalarda İlk Kemoterapiye Tam Yanıtı Etkileyen Faktörler

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Abstract

Objective: We aimed to investigate the factors affecting the complete response (CR) rate and the effect of treatment response on survival in patients with extensive stage-small cell lung cancer (ES-SCLC) who received a combination of cisplatin and etoposide as first-line therapy.

Method: This retrospective analysis included 140 ES-SCLC patients, who were followed in an oncology clinic. Patients were divided into two groups as CR and non-CR according to radiological evaluation after first line chemotherapy. Clinical and demographic characteristics and pre-treatment hemogram parameters were obtained from electronic medical record system.

Results: While CR was seen in 34 (24.3%) of all patients after the first line chemotherapy, 106 (75.7%) patients were in the non-CR group. On univariate analysis, predictors for CR to treatment were the absence of brain metastasis, receiving 6 chemotherapy cycles and good performance status (p<0.001; p=0.020; p=0.001, respectively). In multivariate analysis, the absence of brain metastasis and good performance status were independent predictive factors for CR (p=0.033; p=0.019, respectively). Better treatment response rate to first-line chemotherapy was found to be associated with improved disease-free survival, and overall survival (log-rank p<0.001; log-rank p<0.001, respectively).

Conclusion: Good performance status and the absence of brain metastases were identified as independent predictive factors for CR in ES-SCLC patients at the time of diagnosis. Patients who achieved CR had a significantly longer survival rate than patients with lower treatment response.

Keywords: Chemotherapy, complete response, small cell lung cancer, survival prognosis

Öz

Amaç: Yaygın evre-küçük hücreli akciğer kanseri (ES-SCLC) tanılı olup, ilk basamakta sisplatin ve etoposid kombinasyon kemoterapisi alan hastalarda tedaviye tam yanıtı (CR) etkileyen faktörleri ve tedaviye yanıt düzeyinin sağkalıma etkisini araştırdık.

Yöntem: Bu retrospektif çalışmada ES-SCLC tanılı 140 hasta incelendi. İlk basamak kemoterapi sonrası radyolojik yanıt değerlendirmesine göre CR ve CR olmayan (non-CR) olarak iki grup belirlendi. Klinik, demografik hasta özellikleri ve tedavi öncesi hemogram parametreleri arşivden elde edildi.

Bulgular: Hastaların 34'ü (%24,3) CR, 106 (%75,7) hasta non-CR grubunda yer aldı. Yapılan tek değişkenli analizde tanı anında beyin metastazı yokluğu, 6 kemoterapi siklusu alma ve iyi performans durumu CR için öngörücü faktörler olarak bulundu (sırasıyla p<0,001; p=0,020; p=0,001). Çok değişkenli analizde ise beyin metastaz yokluğu ve iyi performans durumu CR için bağımsız prediktif faktörler olarak saptandı (sırasıyla p=0,033; p=0,019). Ayrıca birinci basamak kemoterapiye verilen yanıt arttıkça hastalıksız sağkalım süresi ve genel sağkalım süresinin uzadığı tespit edildi (sırasıyla log-rank p<0,001; log-rank p<0,001).

Sonuç: Tanı anında beyin metastaz yokluğu ve iyi performans durumu birinci basamak tedaviye tam yanıt için bağımsız prediktif faktörlerdir. Tam yanıta ulaşan hastalar, daha düşük tedavi yanıtına göre önemli ölçüde daha uzun sağkalıma sahiptir.

Anahtar kelimeler: Kemoterapi, küçük hücreli akciğer kanseri, sağkalım, tam yanıt

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Introduction

According to 2021 data, lung cancer is the leading cause of cancer deaths worldwide (1). Despite the advancing medical science, its high mortality continues (2). Small cell lung cancer (SCLC), an aggressive subtype of lung cancer, is a neuroendocrine cancer and accounts for approximately 15% of lung cancers. Up to 60-70% of them are extensive stage-small cell lung cancer (ES-SCLC) at the time of diagnosis (3,4).

There are limited treatment options beneficial for survival in ES-SCLC. The combination of platinum (cisplatin or carboplatin) and etoposide continues to be the standard in initial treatment for SCLC, while the median overall survival (mOS) with this treatment is around 8-13 months (5,6). ES-SCLC patients have been reported to have an objective response rate up to 80% to chemotherapy while 20-30% of patients have a complete response (CR); however, the median response time is short and the 2-year survival rate is less than 10% (7-9). In addition, immunotherapy, PCI, and thoracic radiotherapy are known to prolong survival. Immunotherapies have not yet become a standard in many countries due to the fact that immunotherapies are expensive and therefore difficult to access (10). In treatment guidelines, prophylactic cranial irradiation (PCI) and thoracic radiotherapy are recommended as standard treatment approaches only in patients with a good response to chemotherapy (2,11,12).

In this study, we aimed to examine the factors affecting the treatment response in patients receiving cisplatin and etoposide, the most common regimen used as the first line treatment in ES-SCLC patients, and to evaluate the relationship between treatment response and survival.

Materials and Methods

Patients

In our study, medical records of 140 consecutive patients with ES-SCLC at the time of diagnosis between the years of 2015 and 2020, who were treated in Tekirdağ Namık Kemal University Faculty of Medicine, Department of Medical Oncology, were analyzed retrospectively. Patients who received either etoposide (100 mg/m^2; day 1-3) and cisplatin (75 mg/m^2; day 1 or 25 mg/m^2; day 1-3) combination every 3 weeks chemotherapy were included in the study. The following were used as exclusion criteria: The presence of a different concomitant solid or hematological malignancy, acute infection, no evidence of extensive stage disease according to European Society for Medical Oncology guideline, being under 18 years of age, having an autoimmune disease and a history of immunosuppressive drug use (2). In the staging of the patients, pre-treatment computed tomography, fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography and brain magnetic resonance imaging were used.

Data Collection

Eastern cooperative oncology group (ECOG) performance score, age, gender, smoking status, body mass index (BMI), site of metastasis, presence of superior vena cava syndrome (SVCS), status of receiving PCI, local radiotherapy, number of chemotherapy cycles received, laboratory parameters before initiation of the treatment (neutrophil count, thrombocyte count, hemoglobin value) obtained from blood serum samples were recorded from archive files. Performance scores of the patients were recorded as ECOG 0-1 and 2-3, and their use of cigarette pack/year was separated as over 50 pack/year and below 50 pack/year.

Treatment responses of the patients were determined from their imaging after the chemotherapy regimen was completed. Treatment response was evaluated with computed tomography imaging. As per the RECIST version 1.1, the best response after first-line chemotherapy was categorized as CR, partial response (PR), stable disease (SD) and progressive disease (PD). Intergroup evaluation was done by dividing into two groups as CR and non-CR (partial, stable or progression). Disease-free survival duration (DFS) was considered as the time from onset of disease to the date of radiological progression (according to modified RECIST version 1.1). mOS was calculated as the time from disease diagnosis to the date of death.

Statistical Analysis

SPSS 22.0 for Windows software was used for the statistical analysis. The Fisher's Exact test and the chi-square test for trend were used to assess the association between categorical or ordinal variables and the presence of CR. Univariate and multivariate analyses were performed using the logistic regression model. Survival analysis was done by the Kaplan-Meier method.

Ethical Approval

Ethics approval to carry out the study was provided by Clinical Research Ethics Committee of Tekirdağ Namık Kemal University (date: 27.04.2021, no: 2021.117.04.12).

Results

One-hundred forty patients with ES-SCLC diagnosed according to the criteria included in the study were

included, 109 (77.7%) were male and 31 (22.1%) were female. The median age was 59 years (range: 25-81). Thirty-four (24.3%) of patients achieved a CR to the first line of treatment, 104 (75.7%) patients were in the non-CR group. A total of 54 (41.2) patients received second line of treatment. One-hundred ten (78.6%) of entire patient population died during the study period completed (Table 1).

In the univariate analysis performed, patients without brain metastases, with an ECOG performance score of 0-1 at the time of diagnosis, and who received 6 chemotherapy cycles had a significantly higher CR response (p=0.001, p=0.018, p=0.020, respectively). Besides, the rate of progression seen after first-line chemotherapy, second-line treatment status and the rate of patients who died were higher in patients with non-CR treatment response (p<0.001, p<0.001, respectively). There was no relationship between age, gender, BMI, smoking history, presence of SVCS, extra-brain metastasis area, primary mass location (right/left) and hemoglobin value, platelet value and NLR (neutrophil-lymphocyte ratio) and treatment response to first chemotherapy (p>0.05) (Table 2).

Multivariate analysis of significant factors provided from univariate analyses showed that patients with 0-1 ECOG performance score at the time of diagnosis and those without brain metastases were frequently in the CR group (p=0.019, p=0.033, respectively) (Table 3).

We examined the relationship between the treatment response of the patients to the first chemotherapy and DFS and OS. We divided the initial treatment response into CR, PR, SD and PD. According to the Kaplan-Meier analysis, initial treatment response median DFS (mDFS) was 14.8 months [95% confidence interval (CI) 12.7-15.2], 7 months (95% CI 6.1-7.8), 4 months (95% CI 3.5-4.4), and 1 month, respectively (95% CI 0.6-1.3). There was a statistically significant difference between the groups for mDFS (log-rank p<0.001) (Figure 1). Patients' mOS were 20 months (95% CI 16.6-23.3), 11 months (95% CI 9.1-12.8), 6 months (95% CI 4.8-7.) for the CR, PR, SD and PD groups, respectively and 2 months ((95% CI 1.2-2.7). There was a statistically significant difference between the groups for mOS (long-rank p<0.001) (Figure 2).

Discussion

One-hundred fourty patients diagnosed with ES-SCLC were examined in our study. The aim of this study was to evaluate the relationship between treatment response and survival after first-line chemotherapy in ES-SCLC

Table 1. Patients' characteristics

Characteristic		n	%
Gender	**Female**	**31**	**22.1**
	Male	**109**	**77.9**
Age	**Median (min-max)**	59 (25-81)	
Smoking	**No**	4	2.9
	Yes	136	97.1
Cigarettes package/year	**Over 50**	70	50.0
	Below 50	70	50.0
BMI	**Mean-SD**	24.0±4.5	
ECOG group	**0-1**	105	75.0
	2-3	35	25.0
Localization	**Right**	77	55.0
	Left	63	45.0
SVCS	**No**	131	93.6
	Yes	9	6.4
Brain met	**No**	114	81.4
	Yes	26	18.6
Pleura met	**No**	109	77.9
	Yes	31	22.1
Contra-lung met	**No**	115	82.1
	Yes	25	17.9
Liver met	**No**	102	72.9
	Yes	38	27.1
Adrenal met	**No**	102	72.9
	Yes	38	27.1
Bone met	**No**	69	49.3
	Yes	71	50.7
#Of CT cycles	**Median (min-max)**	6 (1-6)	
Hb (g/dL)	**Mean-SD**	12.6-1.7	
PLT (10^3/uL)	**Mean-SD**	306.2±121.9	
NLR	**Mean-SD**	4.3±3.0	
Response after first series	**CR**	34	24.3
	PR	68	48.6
	SD	15	10.7
	PD	23	16.4
Local RT	**Not received**	112	80.0
	Received	28	20.0
Prophylactic cranial irradiation (PCI)	**Not received**	118	84.3
	Received	22	15.7
Second series treatment	**No**	77	58.8
	Yes	54	41.2
First series treatment	**No**	7	5.0
	Yes	133	95.0
Final status	**Alive**	30	21.4
	Exitus	110	78.6

BMI: Body mass index, ECOG: Eastern cooperative oncology group, SVCS: Superior vena cava syndrome, CT: Chemotherapy, Hb: Hemoglobin, PLT: Levels of platelet, NLR: Neutrophil-to-lymphocyte ratio, CR: Complete response, PR: Partial response, SD: Stable disease, PD: Progressive disease, RT: Radiotherapy

Table 2. Patients' characteristics according to treatment groups

Characteristics*		Complete		Non-complete		p
		n	%	n	%	
Gender	Female	9	26.9	22	20.8	0.485
	Male	25	73.1	84	79.2	
Age	Median (min-max)	58 (25-74)		60 (41-81)		0.798
Smoking	No	0	0.0	4	3.8	0.576
	Yes	34	100.0	102	96.2	
Cigarettes package/ year	Over 50	18	52.9	52	49.1	0.693
	Below 50	16	47.1	54	50.9	
BMI	Mean-SD	24.9±4.1		23.6±4.6		0.935
ECOG group	0-1	33	97.1	72	67.9	**0.001**
	2-3	1	2.9	34	32.1	
Localization	Right	20	58.8	57	53.8	0.607
	Left	14	41.2	49	46.2	
SVCS	No	31	91.2	100	94.3	0.454
	Yes	3	8.8	6	5.7	
Brain met	No	30	88.2	84	79.2	**<0.001**
	Yes	4	11.8	22	20.8	
Pleura met	No	27	79.4	82	77.4	0.802
	Yes	7	20.6	24	22.6	
Contra-lung met	No	30	88.2	85	80.2	0.286
	Yes	4	11.8	21	19.8	
Liver met	No	25	73.0	77	72.6	0.919
	Yes	9	26.0	29	27.4	
Adrenal met	No	26	76.0	76	71.7	0.586
	Yes	8	23.0	30	28.3	
Bone met	No	20	58.8	49	46.2	0.201
	Yes	14	41.2	57	53.8	
#Of CT cycles	Median (min-max)	6 (4-6)		5 (1-6)		0.020
Hb (g/dL)	Mean ± SD	12.8±1.7		12.5±1.7		0.536
PLT (10^3/uL)	Mean ± SD	322-125.6		299.7 (121.1)		0.409
NLR	Mean ± SD	4.2±3.6		4.4±2.7		
Response after first series	CR	34	100.0	0	0.0	**<0.001**
	PR	0	0.0	68	64.2	
	SD	0	0.0	15	14.2	
	PD	0	0.0	23	21.7	
First series treatment	No	7	20.6	0	0.0	**<0.001**
	Yes	27	79.4	106	100.0	
Second series treatment	No	10	29.4	67	68.4	**<0.001**
	Yes	24	70.6	31	31.6	
Final status	Alive	15	44.1	15	14.2	**<0.001**
	Exitus	19	55.9	91	85.8	

*Important values are shown in bold. BMI: Body mass index, ECOG: Eastern cooperative oncology group, SVCS: Superior vena cava syndrome, CT: Chemotherapy, Hb: Hemoglobin, PLT: Levels of platelet, NLR: Neutrophil-to-lymphocyte ratio, CR: Complete response, PR: Partial response, SD: Stable disease, PD: Progressive disease

Table 3. Multivariate analysis for complete response

Characteristics		OR	95% CI for OR		p
ECOG performance score	2-3 vs 0-1	11.670	1.493	91.197	**0.019**
#Of CT cycles received		0.776	0.583	1.033	0.082
Presence of brain metastasis	Yes vs no	2.631	1.082	6.395	**0.033**

Important values are shown in bold. ECOG: Eastern cooperative oncology group, CT: Chemotherapy, CI: Confidence interval, OR: Odds ratio

patients and to evaluate predictive factors for CR. Similar to previous studies, the rate of patients with CR in our study was 24.3% (7-9,13). A significant relationship was found between first-line treatment response (CR, PR, SD or PD) and median OS (mOS) and median DFS (mDFS). One of the main findings was that the more patients responded to the first treatment, the longer they had survival duration. CR treatment response was higher in those with 0-1 ECOG performance score, those without brain metastases at the time of diagnosis, and those who received more first-line chemotherapy cycles. Good performance status and absence of brain metastases were found to be independent predictors for CR in multivariate analysis.

The disadvantage of the performance score is that it can be affected by many acute events during the disease process, but it is known in studies conducted since 1970 that this score is an important prognostic factor in SCLC patients (14-19). However, there are limited studies in the literature comparing the relationship between chemotherapy response and performance status. Tummarello et al. (20) and de Wet et al. (21) showed that performance status was related to treatment response. Consistently, in our study, good performance status was determined as a predictive factor for CR to treatment (20,21). In our study, it was seen that those with better ECOG performance score had significantly more CR to first line chemotherapy than those with poor performance.

In our study, those who received a median of 6 cycles of chemotherapy achieved a higher CR response than those who received a median of 5 cycles of chemotherapy. In previous studies, a comparison of 4-6 cycles was performed and no difference was reported for CR (22,23). The reason for achieving meaningful results in our study may be due to the fact that all patients in the CR group received at least 4 cycles of chemotherapy. This result is consistent with the literature and international guidelines (2,24-27). Nevertheless, the fact that the number of chemotherapy cycles seen as predictive in the univariate analysis was not

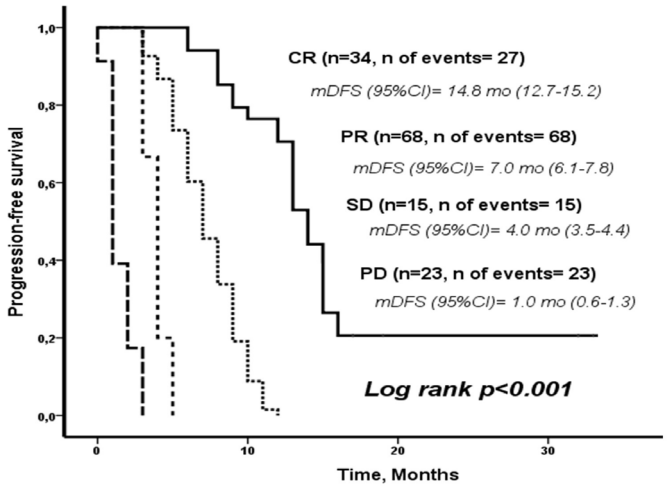

Figure 1. Kaplan-Meier curves displaying the estimated disease free survival probability for 4 different groups of treatment response in ED-SCLC patients receiving cisplatin etoposide combination in the first line therapy

mDFS: Median free survival, CR: Complete response, PR: Partial response, SD: Stable disease, PD: Progressive disease

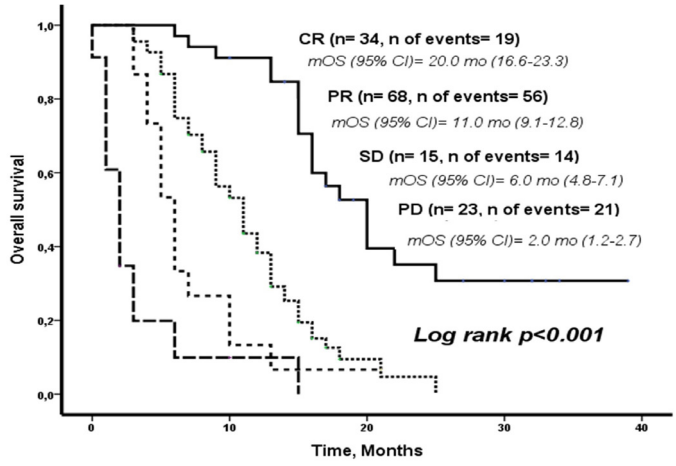

Figure 2. Kaplan-Meier curves displaying the estimated overall survival probability for 4 different groups of Treatment Response in ED-SCLC patients receiving cisplatin etoposide combination in the first line therapy

mDFS: Median free survival, CR: Complete response, PR: Partial response, SD: Stable disease, PD: Progressive disease

found as an independent predictive factor in the multivariate analysis and this may be due to its high correlation with the ECOG, in which the number of chemotherapy cycles received is analyzed together.

In the studies of Bremnes et al. (28), Früh et al. (24), and Gerdan et al. (29), the presence of brain metastasis was reported as an important prognostic factor for ES-SCLC. In our study, the presence of brain metastases at the time of diagnosis predicted poor response to first-line treatment response. This may be due to the low chemotherapy efficacy in the treatment of brain metastases due to the blood-brain barrier, and therefore not to show its maximum effect or from the effect of brain metastasis on performance and treatment compliance (30).

In previous studies, there are consistent results with higher treatment response and better survival of patients (27,31-33). However, there are also reports on that the first line treatment response does not benefit survival in this disease with rapid recurrence (34,35). In our study, it was observed that as the first line treatment response increased, the patients reached better mOS and mDFS times. Accordingly, the highest mOS and mDFS were observed in patients with CR response, while the lowest survival durations were found in patients with PD responses. There is no consensus on this issue in the literature and it still remains controversial. This situation may depend on the characteristic of the tumor, the characteristics of the selected patients or the status of receiving advanced chemotherapy and the chemotherapy regimens chosen.

There are many studies in the literature reporting that NLR and PLR, which are considered systemic inflammatory markers, are prognostic for ES-SCLC (14,19,36,37). In the studies of Torres-Durán et al. (38) and Huang and Shi (39), smoking status has been reported as a poor prognostic factor. In addition, there are several studies reporting the prognostic role of bone, liver and other organ metastasis (28,40). In our study, these factors were also included in our comprehensive analysis; however, they were not found to be independent predictive factors for CR.

Study Limitations

Some factors that were previously determined to be prognostic and predictive could not be examined (e.g. uric acid, neuron-specific enolase, weight loss, alkaline phosphatase, lactate dehydrogenase), which is among the limiting factors of our study, because it was a single-center and retrospective study. However, our study analyzed patient and treatment characteristics more comprehensively than previous studies. In addition, detailed analysis of treatment groups and sole inclusion of patients receiving cisplatin and etoposide combination therapy for survival analysis evaluation increased the sensitivity of our evaluation.

Conclusion

This study demonstrated that better performance score and brain metastasis status at the time of diagnosis are independent predictive factors for CR, which is the main

treatment goal in ES-SCLC patients. Prognostic factor analysis and investigation of effective treatments are needed, as overall survival times are short even if patients diagnosed with ES-SCLC are treated. Finding predictive markers with such studies may be useful both for patient classification in future studies and for patient-specific treatment and follow-up decisions.

Ethics

Ethics Committee Approval: Ethics approval to carry out the study was provided by Clinical Research Ethics Committee of Tekirdağ Namık Kemal University (date: 27.04.2021, no: 2021.117.04.12).

Informed Consent: Patient consent was not required for this study.

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Authorship Contributions

Concept: E.Ç., E.S.Ş., Design: E.Ç., Y.İ., A.S., Data Collection or Processing: E.Ç., A.S., Y.İ., Analysis or Interpretation: E.Ç., Y.İ., E.S.Ş., Literature Search: E.Ç., A.S., Writing: E.Ç., E.S.Ş., Manuscript Review and Revisation: E.Ç., Y.İ., A.S., E.Ş.S.

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