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EFFICACY OF SECOND-LINE TREATMENTS IN LUNG AND EXTRAPULMONARY NEUROENDOCRINE CARCINOMAS

AKCİĞER VE AKCİĞER DIŞI NÖROENDOKRİN KARSİNOMLARINDA İKİNCİ BASAMAK TEDAVİ ETKİNLİĞİ

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ABSTRACT

Objective: The objective of this study was to explore the efficacy of second-line treatments, given the ambiguity surrounding subsequent treatments due to rapid disease progression and patient scarcity.

Materials & Methods: A retrospective study was conducted at the XXXX City Training and Research Hospital Medical Oncology Outpatient Clinic from 2017 to 2021, encompassing 991 patients diagnosed with lung cancer and NEC. Data from 304 patients, specifically diagnosed with NEC/Small-cell lung cancer, were analyzed. All patients underwent cisplatin-etoposide as their first-line treatment, with 35 of these receiving a second-line treatment.

Results: Of the analyzed patients, 91 were diagnosed with lung-derived-NEC and 35 with extrapulmonary-NEC. The median progression-free survival (PFS) post the first-line treatment was 7.4 months. A total of 35 patients received second-line chemotherapy. The median PFS2 was 5.1 months and 6.6 months in patients who received irinotecan-based chemotherapy and cisplatin-etoposide therapy, respectively(p:0.86). There was no significant difference between patients with lung-derived-NEC and patients with extrapulmonary-NEC in PFS2 or OS values.

Conclusion: The study underscores the lack of a standardized second-line treatment for small-cell lung cancer. However, data suggests that cisplatin-etoposide therapy might be effective as a second-line treatment, especially for patients relapsing after more than six months post the initial treatment. The outcomes align with other research, indicating a decline in overall survival as the Ki-67 index value increases.

Key words: Neuroendocrine tumors, Neuroendocrine carcinoma, Cisplatin-etoposide therapy, Second-line treatment, Ki-67 index.

ÖZET

Amaç: Bu çalışmanın amacı, hızlı hastalık ilerlemesi ve hasta azlığı nedeniyle sonraki basamaklardaki tedavi belirsizliği göz önüne alındığında, ikinci basamak tedavilerin etkinliğini araştırmaktır.

Gereç ve Yöntem: Adana Şehir Eğitim ve Araştırma Hastanesi Tıbbi Onkoloji Polikliniği'nde 2017-2021 yılları arasında akciğer kanseri ve NEK tanısı alan 991 hastayı kapsayan retrospektif bir çalışma . NEC/Küçük hücreli akciğer kanseri tanısı alan 304 hastanın verileri analiz edildi. Tüm hastalara birinci basamak tedavi olarak sisplatin-etoposid uygulandı ve bunların 35'i ikinci basamak tedaviyi aldı.

Bulgular: Analiz edilen hastaların 91'ine akciğer kaynaklı NEK, 35'ine ekstrapulmoner NEK tanısı mevcuttu. Birinci basamak tedavi alanlarda ortalama progresyonsuz sağkalım (PFS) 7,4 aydı. Toplam 35 hasta ikinci basamak kemoterapi aldı. İrinotekan bazlı kemoterapi ve sisplatin-etoposid tedavisi alan hastalarda medyan PFS2 sırasıyla 5,1 ay ve 6,6 ay idi(p:0,86). Akciğer kaynaklı NEC'li hastalar ile ekstrapulmoner NEC'li hastalar arasında PFS2 veya OS değerlerinde anlamlı bir fark yoktu.

Sonuç: Çalışma, küçük hücreli akciğer kanseri için standardize edilmiş ikinci basamak tedavinin eksikliğinin altını çizmektedir. eriler, sisplatin-etoposid tedavisinin, özellikle ilk tedaviden altı ay sonra tekrarlayan hastalar için ikinci basamak tedavi olarak etkili olabileceğini düşündürmektedir. Sonuçlar diğer araştırmalarla uyumludur ve Ki-67 indeks değeri arttıkça genel hayatta kalma oranının azaldığını göstermektedir.

Anahtar Kelimeler: Nöroendokrin tümörler, Nöroendokrin karsinom, Sisplatin-etoposid tedavisi, İkinci basamak tedavi, Ki-67 indeksi.

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INTRODUCTION

Neuroendocrine tumors (NETs) often originate from endocrine and neural system cells in the pancreas and lungs. The World Health Organization (WHO) has divided NETs into three categories(La Rosa & Uccella, 2020). Grade 3 NETs are called neuroendocrine carcinoma (NEC) and often have a Ki-67 index above 20%(La Rosa & Uccella, 2020).

NECs can develop from lung and extrapulmonary organs. Lung-derived NECs (LD-NECs) are divided into large-cell and small-cell NECs. Small-cell lung cancer (SCLC) constitutes the majority of NECs in the lung. Extrapulmonary NECs (EP-NEC), which are rare, can develop from many organs but mainly originate from the gastrointestinal system (Strosberg et al., 2010; Walenkamp, Sonke, & Sleijfer, 2009). The origin of approximately 30% of EP-NECs cannot be determined (Klöppel, Heitz, Capella, & Solcia, 1996; Walenkamp et al., 2009). LD-NECs and EP-NECs have similar histological features(Thomas et al., 2019). EP-NEC treatment is mainly planned by drawing inferences from LD-NECs(Ramella Munhoz et al., 2013; Sorbye et al., 2013). Although the curative treatment is surgery, systemic therapy comes to the fore as approximately 85% of the patients are detected in the advanced stage(Garcia-Carbonero et al., 2016).

The established first-line treatment in patients with a diagnosis of NEC is cisplatin-etoposide therapy(Pujol et al., 2015). However, the treatments given after the cisplatin-etoposide therapy are not well-established since prospective studies on second-line treatments and the treatments to be administered thereafter cannot be conducted due to the low number of patients and rapid progression of the disease. In this context, this study was conducted to investigate the second-line treatments administered to patients with LD-NEC and EP-NEC at the metastatic stage, their response to these treatments, and the efficacies of these treatments.

MATERIALS AND METHODS

The population of this retrospective study consisted of 991 patients registered to the Adana City Training and Research Hospital Medical Oncology Outpatient Clinic diagnosed with lung cancer and NEC between January 1st, 2017, and June 1st, 2021. Of these patients, the data of 304 patients who were biopsied from radiologically determined primary cancer sites or metastatic sites and pathologically diagnosed with NEC/SCLC were analyzed. The lung, liver, pancreas, esophagus, stomach, small intestine, colon, rectum, prostate, and adrenal glands were considered the primary sites where NEC could develop, while the brain and bones were not considered the primary sites where NEC could develop. In this context, 140 patients who had masses in the lungs and other organs with radiologically confirmed simultaneous primary NEC at the time of diagnosis were excluded from the study. The treatments received by the remaining 164 patients were evaluated. Of the patients, 38 patients who did not receive or accept to receive treatments were excluded from the study. In the end, the study sample consisted of 126 patients who received at least one cycle of chemotherapy and whose treatment responses were evaluated objectively by radiological methods or positron emission tomography/computed tomography (PET/CT). Ethical approval was obtained from Adana City Training and Research Hospital with number 17.06.2021/1458

All patients received cisplatin-etoposide therapy as the first-line treatment. The treatment the patients would receive as second-line treatment was decided based on the drug-free time until relapse. Accordingly, patients who relapsed after six months were given cisplatin-etoposide therapy, those who relapsed between 3-6 months were given cisplatin-irinotecan combination therapy, and those who relapsed before three months were given stand-alone irinotecan therapy. The study sample was divided into two groups depending on the treatments received by the patients. Accordingly, patients who received cisplatin-etoposide therapy as the second-line treatment were included in Group 1, and those who received irinotecan-based treatment, i.e., stand-alone irinotecan therapy or irinotecan-cisplatin combination therapy, as the second-line treatment were included in Group 2. Progression-free survival 1 (PFS1) was calculated from the time of diagnosis to the time of radiologically demonstrated progression or the time of death from any cause, whereas PFS2 was calculated from the date of radiological progression after first-line chemotherapy to the time of radiological progression detected while receiving second-line chemotherapy or the time of death from any cause. Overall survival (OS) was calculated from the time of diagnosis to the time of death from any cause.

Statistical Analysis

Statistical analyses of the collected data were performed using the SPSS 21.0 (Statistical Product and Service Solutions for Windows, Version 21.0, IBM Corp., Armonk, NY, U.S., 2012) software package. In comparing the median and mean values between the two groups, Spearman's correlation analysis was performed for non-normally distributed data or data involving less than 30 people, and Pearson's correlation analysis was performed for normally distributed data. Pearson's chi-square and Fischer's exact tests were used to evaluate clinical parameters and laboratory data. Kaplan Meier curves were used to assess the correlations between clinical parameters and OS and PFS.

RESULTS

Of the 126 patients, 103 (81.7%) male and 23 (18.3%) female, included in the study, 91 (72.2%) were diagnosed with LD-NEC and 35 (27.8%) with EP-NEC. The median age of the patients at the time of diagnosis was 63 (min.34, max.84) years. The mean age of LD-NEC and EP-NEC patient groups was 61.7 ± 9.9 years and 56.3 ± 9.2 years, respectively. The median OS and PFS of the patients were 12.6 (min. 1.1, max. 69.8) months and 7.4 (min. 1.1, max. 69.5) months, respectively. The analysis of patients' pathological and immune-histochemical data revealed a mean Ki-67 index of 74.8% ± 18.8%. Further analysis of patients' pathological data revealed that the thyroid transcription factor-1 (TTF-1) positivity was significantly higher in patients with LD-NEC (p=0.011) than in patients with EP-NEC and that there was no significant difference between patients with LD-NEC and patients with EP-NEC in Ki-67 index or neuron specific enolase (NSE), chromogranin, and synaptophysin positivity. The distribution of metastases at the time of diagnosis is given in Table-1.

Table 1. Clinical, demographic, laboratory and pathological data of patients receiving first-line therapy

		LD-NEC	EP-NEC	p
Number of patients (%)		91 (%72.2)	35(%27.8)	
Age (years) mean ± SDS		62.6 ± 9.4	61.6 ± 12.3	0.610
Gender	Man (n)	78 (%85.7)	25 (%71.4)	0.109
	Woman (n)	13 (%14.3)	10 (%28.6)	
LDH	Above Normal (n)	61 (%67)	24(%68.6)	0.869
	Normal (n)	30 (%33)	11 (%31.4)	
Ki 67	> % 55 (n)	51 (%88)	23(%76.7)	0.221
	<%55 (n)	7 (%12)	7(%23.3)	
Synaptophysin	Positive (n)	63 (%96.9)	31 (%100)	0.374
	Negative (n)	2 (%3.1)	0 (%0)	
CD56	Positive (n)	30 (%96.9)	14(%73.7)	0.176
	Negative (n)	4 (%88.2)	5(%26.3)	
NSE	Positive (n)	7 (%58.3)	6 (85.7)	0.216
	Negative (n)	5 (%41.7)	1(%14.3)	
CK7	Positive (n)	14 %66.7	10 (%41.7)	0.168
	Negative (n)	7 %33.3	14 (%58.3)	
TTF1	Positive (n)	51 (%83.6)	13 (%54.2)	0.011
	Negative (n)	10 (%16.4)	11 (%45.8)	
Chromogranin	Positive (n)	37 (%62.7)	24 (%77.4)	0.156
	Negative (n)	22 (%37.3)	7 (% 22.6)	
Brain metastasis at the time of diagnosis (n)		21(%23)	3 (%8.5)	0.048
Liver metastasis at diagnosis (n)		0	9 (%25.7)	<0.001
Bone metastasis at the time of diagnosis (n)		33 (%36.3)	13 (%37.1)	

*LD-NEC: Lung-derived neuroendocrine tumor, EP-NEC: Extrapulmonary neuroendocrine tumor, SDS: standard deviation score, LDH: Lactate dehydrogenase, NSE: Neuron-specific enolase, TTF 1: Thyroid transcription factor 1

All (n=126, 100%) patients received cisplatin-etoposide therapy as the first-line treatment. No patient was given immunotherapy as the first-line treatment since immunotherapies are not reimbursed by the Social Security Institution in Turkey. The median PFS was 7.4 (min. 1.1, max. 69.5) months in those who received first-line treatment (Figure-1).

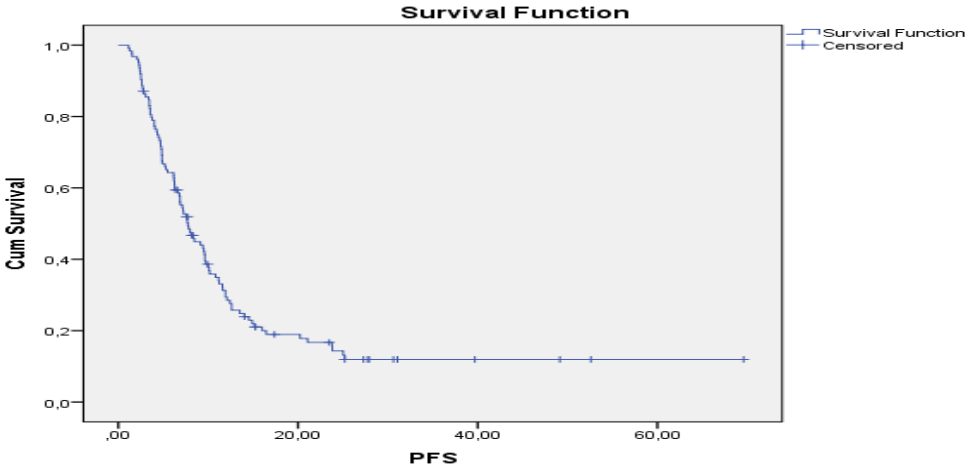

Figure-1. Progression free survival (months) of patients who received first line chemotherapy
*PFS: progression-free survival, Cum Survival: cumulative survival

Seven patients were started on maintenance oral etoposide therapy after first-line treatment. Of these patients, five received irinotecan-based treatment as second-line chemotherapy, and two received cisplatin-etoposide therapy since they received maintenance oral etoposide therapy for more than six months. PFS1 was 11.9 (min. 6.2, max. 23.7) months in those who received maintenance etoposide therapy and 8.11 (min. 3.5, max. 20.2) months in those who did not receive maintenance etoposide therapy. Additionally, PFS2 was 4.8 (min. 2.8, max. 29.6) months in those who received maintenance etoposide therapy and 5.6 (min. 0.3, max. 31) months in those who did not receive maintenance etoposide therapy.

A total of 35 patients, 30 (85.7%) male, and 5 (14.3%) female, received second-line chemotherapy. Of these patients, 27 (77.1%) received irinotecan-based chemotherapy, and 8 (22.9%) received cisplatin-etoposide chemotherapy once more. The pathology data of the patients who received second-line chemotherapy are given in Table-2. After the end of the first-line chemotherapy, the median time to the start of irinotecan-based chemotherapy as the second-line treatment was 2.0 (min. 0.4, max. 5.3) months, and the median time to the start of cisplatin-etoposide therapy as the second-line treatment was 11.7 (min. 6.5, max. 20.7) months.

The median PFS2 was 5.1 (min. 0.5, max. 31.6) months and 6.6 (min. 0.3, max. 13.1) months in patients who received irinotecan-based chemotherapy and cisplatin-etoposide therapy, respectively, as the second-line treatment. There was no significant difference between patients with LD-NEC and patients with EP-NEC in PFS2 or OS values (Figures 2 and 3).

Table 2. Clinical, demographic, laboratory and pathological data of patients receiving second-line therapy

		LD-NEC	**EP-NEC**
Number of patients (%)		27 (%77.1)	8(%22.9)
Age (years) mean ± SDS		61.7 ± 9.9	56.3 ± 9.2
Gender	Man (n)	22(%81.4)	8 (%100)
	Woman (n)	5 (%18.6)	0
LDH	Above Normal (n)	20 (%74.1)	4(%50)
	Normal (n)	7 (%25.9)	4(%50)
Ki 67	> % 55 (n)	14(%87.5)	5(%71.4)
	<%55 (n)	2(%12.5)	2(%28.6)
Synaptophysin	Positive (n)	18 (%100)	7(%87.5)
	Negative (n)	0	1(12.5)
CD56	Positive (n)	8 (%88.9)	5(%83.3)
	Negative (n)	1 (%11.1)	1(%16.7)
CK7	Positive (n)	4 (%80)	3(%50)
	Negative (n)	1 (%20)	3(%50)
TTF1	Positive (n)	14 (%82.1)	4(%66.6)

	Negative (n)	3 (%17.6)	2(%33.3)
Chromogranin	Positive (n)	10 (%58.8)	5(%71.4)
	Negative (n)	7 (%41.2)	2(%28.6)
Brain metastasis at the start of second-line therapy (n)		6 (%22.2)	0
Liver metastasis at the start of second-line therapy (n)		0	2 (%25)

*LD-NEC: Lung-derived neuroendocrine tumor, EP-NEC: Extrapulmonary neuroendocrine tumor, SDS: standard deviation score, LDH: Lactate dehydrogenase, NSE: Neuron-specific enolase, TTF 1: Thyroid transcription factor 1

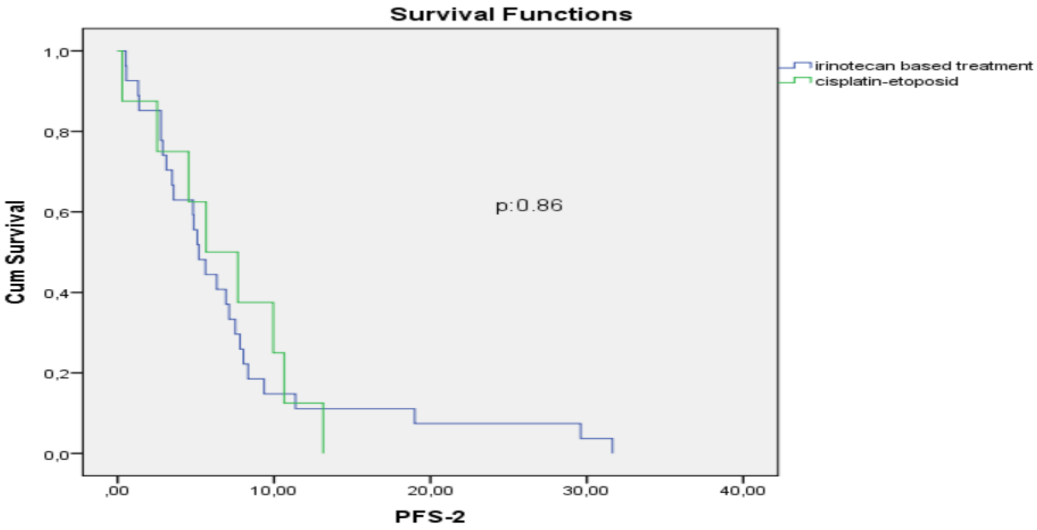

Figure-2. Progression free survival (months) of patients who received second line chemotherapy
*PFS2: progression-free survival, Cum Survival: cumulative survival

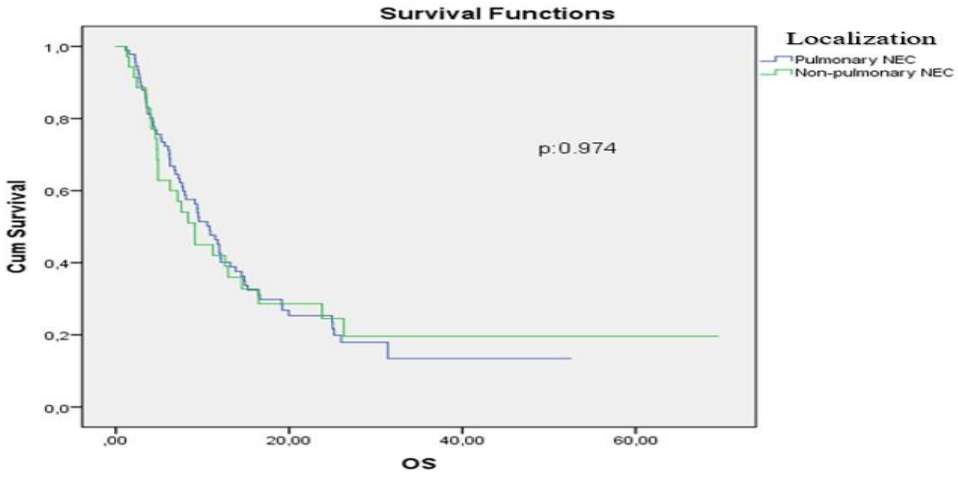

Figure-3. Overall survival (months) of patients according to tumor location
*OS: Overall survival, Cum Survival: cumulative survival

DISCUSSION

The standard treatment currently used in the treatment of SCLC is a combination of platinum-etoposide therapy and immunotherapy. However, there is no standard treatment regimen used as the second-line

treatment. Although it is recommended to use the first-line treatment as the second-line treatment in patients who have had more than six months to relapse without treatment, no specific treatment regimen is recommended for use in patients who have had less than six months to relapse without treatment. Nevertheless, irinotecan-based treatments are commonly used in cases where relapse occurred in less than six months without treatment. All patients included in this study received cisplatin-etoposide therapy as the first-line treatment. Of these patients, 35 received second-line treatment. Most patients received irinotecan-based therapy as the second-line treatment since they had relapsed in less than six months without treatment. However, data suggests that cisplatin-etoposide therapy might be effective as a second-line treatment, especially for patients relapsing after more than six months post the initial treatment.

The study conducted by Horn et al. with NEC patients investigating the efficacy of immunotherapy as the first-line treatment revealed that the addition of etezoluzumab to the chemotherapy significantly prolonged PFS and OS by 0.9 months and two months, respectively (p:0.02 and p:0.007, respectively)(Horn et al., 2018). In comparison, in this study, the PFS of patients with LD-NEC was found to be 7.4 months longer than that of patients with EP-NEC. However, this finding was attributed to the low number of metastatic sites in patients with LD-NEC. The outcome would probably have been different had patients been given immunotherapy in addition to chemotherapy.

NECs and SCLCs are high-grade tumors with a high proliferative index. In the literature, there is not much information about response rates according to the Ki-67 index values. Some studies reported that patients with high Ki-67 index values had longer PFS yet shorter OS after chemotherapy(de M Rêgo et al., 2017). In comparison, in this study, there was no significant difference between the Ki-67 index values of patients with LD-NEC and EP-NEC (p=0.221). There was also no significant correlation between Ki-67 index values and PFS or OS (p:0.411). Sorbye et al. reported the mean Ki-67 index value of the patients as 55% using receiver operating characteristic (ROC) curve analysis(Sorbye et al., 2013). They found that patients with a Ki-67 index value lower than 55% had lower treatment response rates, and patients with a Ki-67 index value higher than 55% had shorter OS. In comparison, in this study, the median OS was 12.6 (min. 1.1, max. 69.8) months, and in line with Sorbye et al.'s study, patients with a Ki-67 index value higher than 55% had shorter OS than those with a Ki-67 index value lower than 55%. Taken together, these findings indicate that the OS decreases as the Ki-67 index value increases. The increase in cell proliferation might be due to achieving good treatment responses with conventional chemotherapies that are effective in the cell division phase and to the rapid progression of the disease after relapse resulting in death.

The median PFS was 7.4 (min. 1.1, max 69.5) months and 5.1 (min. 0.5, max. 31.6) months in patients that received first-line treatment and second-line treatment, respectively. There was no significant correlation between PFS and Ki-67 index value (p:0.765). The efficacy of the second-line treatment seems to decrease compared to the first-line treatment regardless of the type of treatment used as the second-line treatment, as there was no significant difference between Groups 1 and 2 in PFS (p=0.86). This finding may be attributed to the relatively small sample size. Then again, the fact that PFS was found to be longer in patients who received cisplatin-etoposide therapy as the second-line treatment suggests that the same treatment should be repeated in suitable patients as the second-line treatment. The finding that patients who received irinotecan-based therapy as the second-line treatment had shorter PFS may be attributed to the low efficacy of this group of drugs or their use in patients with early relapse who are likely to be resistant to chemotherapy.

C. Zhang et al. demonstrated that maintenance etoposide therapy prolonged PFS in patients who responded to first-line treatment(Zhang et al., 2021). In comparison, in this study, patients who received maintenance oral etoposide therapy had a prolonged PFS1 and a shortened PFS2. There are a limited number of second-line treatments available for NEC patients. In addition, the efficacies of these second-line treatments are also not sufficient. In this context, the prolongation of PFS with the use of maintenance etoposide therapy after first-line treatment in this study indicates that maintenance etoposide therapy may be used more frequently in this patient population.

Hanna et al. reported the rates of patients who survived the first year and second year after receiving cisplatin-etoposide therapy as the first-line treatment as 35.1% and 7.9%, respectively(Hanna et al., 2006). In comparison, in this study, the rates of patients who survived the first year and second year after receiving cisplatin-etoposide therapy as the first-line treatment were 44.5% and 27.6%, respectively. The higher survival rates in this study compared to Hanna et al.'s study may be attributed

to the lower number of visceral organ metastases in the patients included in this study at the time of diagnosis compared to the other study.

NECs originating from the gastrointestinal tract featuring diffuse liver metastasis are rarely encountered in clinical practice. Treatment decisions for this patient group are commonly made by drawing inferences from studies on NECs and SCLCs. Yamaguchi et al. reported the PFS of the patients who received cisplatin-irinotecan combination therapy and stand-alone irinotecan therapy for NECs originating from the digestive system as the second-line treatment at 2.2 months and 4.8 months, respectively(Yamaguchi et al., 2014). They also reported a significant correlation between high-low lactate dehydrogenase (LDH) levels and shorter OS (p=0.002). In line with the findings of the said study, in this study, the median PFS2 of the patients who received irinotecan-based chemotherapy for NEC of gastrointestinal origin was 4.8 (min. 1.3, max. 29.6) months. Additionally, the OS and PFS1 were 10.1 ± 8.3 months and 7.7 ± 6.1 months in patients receiving first-line treatment with LDH levels higher than the upper limit of normal at the time of diagnosis, and 17.9 ± 14.7 months and 15.8 ±14.9 months in patients with normal LDH (p=0.001 for both cases), supporting the significant correlation between high LDH levels and shorter survival.

In conclusion, the findings of this study showed that patients who responded to cisplatin-etoposide treatment as the first-line treatment responded better to cisplatin-etoposide treatment also as the second-line treatment than irinotecan-based treatments, and their PFS was also longer. Therefore, cisplatin-etoposide treatment should be repeated as the second-line treatment in patients who have had more than six months to relapse without treatment.

HIGHLIGHTS

1. Neuroendocrine tumors (NETs) predominantly originate from endocrine and neural system cells in the pancreas and lungs, with Grade 3 NETs, termed as neuroendocrine carcinoma (NEC), often having a Ki-67 index above 20%.
2. A retrospective study at the Adana City Training and Research Hospital Medical Oncology Outpatient Clinic from 2017 to 2021 analyzed data from 304 patients diagnosed with NEC/SCLC out of 991 patients with lung cancer and NEC.
3. All patients underwent cisplatin-etoposide as their first-line treatment, with the median progression-free survival (PFS) post this treatment being 7.4 months.
4. For those who received a second-line treatment, the PFS reduced to 5.1 months, with many patients relapsing within six months post initial treatment being administered irinotecan-based therapy.
5. The study emphasizes the need for a standardized second-line treatment for SCLC, suggesting the potential efficacy of cisplatin-etoposide therapy, especially for patients relapsing after more than six months post the initial treatment.

Author Contributions

Plan, design: S.A.;T.Ç.; Materials, methods, and data collection: O.K ; A.Z.B.; Analysis and interpretation: T.K.; Z.A.T ; Writing and critical assessment: S.A.;B.B.D.

Conflict of interest

There is no conflict of interest to declare in this study.

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