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Research Article

Does using atezolizumab with more combination chemotherapy prolong survival in small cell lung cancer?

Küçük hücreli akciğer kanserinde daha fazla kombine kemoterapi ile atezolizumab kullanımı sağkalımı uzatır mı?

Bilgin Demir*[1], Omer Faruk Akgul[2], Ali Aytac[2], Ayhan Aclan[2], Onur Yazdan Balcik[3], Mehmet Uzun[4], Esin Oktay[2]

[1]Department of Medical Oncology, Ataturk State Hospital, Aydın,Turkey,
[2]Department of Medical Oncology, Aydin Adnan Menderes University, Aydın, Turkey,
[3]Department of Medical Oncology Mardin Training and Research Hospital Mardin, Turkey,
[4]Department of Medical Oncology, Dokuz Eylül University, Izmir, Turkey.

Abstract

Aim: For nearly 50 years, the standard first-line treatment for small cell lung cancer (SCLC) has been platinum-based chemotherapy combined with etoposide regimen. The use of atezolizumab in combination with chemotherapy in the first-line treatment of extensive-stage SCLC has recently been shown to improve survival in a randomized trial. Patients with SCLC not treated with immunotherapy received standard 6 cycles of platinum-based chemotherapy with the most effective survival results, whereas in the randomized trial of atezolizumab, standard 4 cycles of chemotherapy were administered. This retrospective study aims to present real-life data of atezolizumab combined with 6 cycles of chemotherapy in the first-line treatment of extensive-stage SCLC.

Material and Methods: The study included patients diagnosed with disseminated SCLC in our clinic who received a minimum of 6 cycles of treatment with carboplatin-etoposide plus atezolizumab in the first-line induction phase. Patients who completed the induction phase received atezolizumab 1200 mg every 3 weeks in the maintenance phase. Patients who received less than 6 cycles of chemotherapy combined with atezolizumab in the induction phase and patients with missing laboratory data were excluded from the study. Characteristics of the patients, treatments administered, response rates and survival data were analyzed. Kaplan-Meier test was used to determine survival data and the effects of metastasis sites were analyzed using log-rank test.

Results: Twenty-four patients fulfilling the criteria were included. The median age was 64 years and two thirds had comorbid disease. The median number of chemotherapy cycles was 6 (6-12) and atezolizumab cycles was 8 (6-54). After a median follow-up of 9.4 months, the median progression-free survival (PFS) and overall survival (OS) were 9.5 months (95% CI 0.0-25.8) and 30.1 months (95% CI 3.26-57.004), respectively. The overall response rate was 87.5%. There was no significant difference between the number of metastatic sites (p = 0.77) and OS. Grade 3 side effects were observed in more than half of the patients. The most common side effects were hematological toxicities, and all toxicities were manageable.

Conclusion: These real-life data confirm the efficacy and safety of atezolizumab combined with at least six cycles of chemotherapy in the induction phase in the first-line treatment of extensive-stage SCLC.

Keywords: Atezolizumab, cancer, chemotherapy, immunotherapy, lung

Corresponding Author*: Bilgin Demir, Department of Medical Oncology, Ataturk State Hospital, Aydın, Turkey.
Orcıd: 0000-0003-4380-9419
E-mail: bilgin287@hotmail.com
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Öz

Amaç: Küçük hücreli akciğer kanserinde (KHAK) yaklaşık 50 yıldır standart birinci basamak tedavi platin bazlı kemoterapi ile kombine etoposid rejimidir. Atezolizumabın yaygın evre KHAK birinci basamak tedavisinde kemoterapi ile kombine kullanımı yakın zamandan sağkalımı iyileştirdiği randomize bir çalışmada gösterilmiştir. Immunoterapi tedavisi uygulanmayan KHAK'li hastalara standart 6 kür platin bazlı kemoterapi uygulanarak en etkili sağkalım sonuçlarına ulaşılırken, atezolizumabın randomize çalışmasında standart 4 kür kemoterapi uygulanmıştır. Bu retrospektif çalışma, yaygın evre KHAK birinci basamak tedavisinde 6 kür kemoterapi ile kombine atezolizumabın gerçek yaşam verilerini sunmayı amaçlamaktadır.

Gereçler ve Yöntemler: Çalışmaya kliniğimizdeki yaygın evre KHAK tanılı ve birinci basamak indüksiyon fazında karboplatin-etoposid artı atezolizumab ile kombine minimum 6 siklus tedavi alan hastalar dahil edildi. İndüksiyon fazı tamamlanan hastalara idame fazında atezolizumab 1200 mg 3 haftada bir uygulandı. İndüksiyon fazında 6 siklus atezolizumab ile kombine kemoterapiden az tedavi alan hastalar ile laboratuvar verileri eksik olan hastalar çalışma dışı bırakıldı. Hastaların özellikleri, uygulanan tedaviler ve tedaviye yanıt oranları ile sağ kalım verileri incelendi. Sağkalımı verilerini belirlemek için Kaplan-Meier testi kullanıldı ve metastaz bölgelerinin etkileri log-rank testi kullanılarak analiz edildi.

Bulgular: Kriterleri karşılayan 24 hasta dahil edildi. Ortanca yaş 64 idi ve üçte ikisinde komorbid hastalık vardı. Medyan kemoterapi döngüsü sayısı 6 (6-12) ve atezolizumab döngüsü 8 (6-54) idi. Medyan 9,4 aylık takipten sonra medyan progresyonsuz sağkalım (PFS) ve genel sağkalım (OS) sırasıyla 9.5 ay (%95 GA 0.0-25.8) ve 30,1 aydı (%95 GA 3.26-57.004). Genel yanıt oranı %87.5 idi. Metastatik bölge sayısı ($p = 0.77$) ile OS arasında anlamlı bir fark bulunamadı. Hastaların yarısından fazlasında derece 3 yan etki gözlendi. En sık yan etkiler hematolojikdi ve toksisiteler yönetilebilirdi.

Sonuç: Bu gerçek yaşam verileri, yaygın evre KHAK birinci basamak tedavisinde indüksiyon fazında en az altı siklus kemoterapi ile kombine atezolizumab etkiliğini ve güvenliliğini doğrulamaktadır.

Anahtar Kelimeler: Atezolizumab, kanser, kemoterapi, immünoterapi, akciğer

Introduction

Lung cancer is the leading cause of cancer death. According to its biology, treatment and prognosis, it is divided into 2 classes by the World Health Organization: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). SCLC accounts for approximately 15% of all lung cancer cases. The disease is classified into two stages: limited and extensive. Small Cell Lung Cancer is a chemotherapy (CT) sensitive cancer, but differs from other types of lung cancer due to its rapid doubling time and early development of extensive disease. Approximately two thirds of patients have diffuse stage disease at the time of diagnosis and the number of early-stage patients eligible for multimodality treatment is quite low.1,2

The median life expectancy in SCLC without treatment is 2-4 months after diagnosis and 6-12 months with treatment. The overall 5-year survival rate is around 5-10%. Compared to non-small cell lung cancer, treatment options are fewer and prognosis is worse. The standard first-line treatment for nearly 50 years has been a regimen of etoposide combined with platinum-based CT. Although this treatment has a rapid response rate, the median progression-free survival (PFS) is 5.5 months and the median overall survival (OS) is 10 months, because when the disease is refractory to first-line platinum combination therapy, subsequent-line therapies are not effective enough.3-5

Atezolizumab, a monoclonal antibody against programmed cell death ligand 1 (PD-L1), has become an important part of treatment in most types of cancer in recent years. Immunotherapy agents had antitumor activity in SCLC, but did not provide a survival advantage after first-line CT. However, combining PD-1/PD-L1 pathway inhibitors with CT in first-line treatment improved overall survival in patients with extensive-stage SCLC.6-8 In SCLC immunotherapy studies, first durvalumab and then atezolizumab showed survival benefit when combined with CT in the first-line setting and were accepted as the preferred treatments for extensive-stage disease in the guidelines.7,9

Patients with SCLC who are not treated with immunotherapy have the most effective survival results with standard 6 cycles of platinum-based KT. In the IMpower133 trial, a survival benefit was demonstrated by adding atezolizumab to the standard 4 cycles of carboplatin-etoposide combination CT.

Although this benefit has been demonstrated in randomized controlled trials, investigation of real-life efficacy and safety is important to confirm the results and has not been extensively studied. This retrospective study aims to present real-life data of 6 cycles of CT combined with atezolizumab in the first-line treatment of extensive SCLC.

Material and Methods

Study Population and Data Collection

Patients diagnosed with extensive SCLC at the Medical Oncology Clinic of Aydın Adnan Menderes University were included in this study. Inclusion criteria were having histologically or cytologically confirmed extensive stage SCLC according to the modified version of the Veterans Administration Lung Cancer Study Group (VALSG) staging system, being 18 years of age or older, and receiving a minimum of 6 cycles of treatment combined with carboplatin-etoposide plus atezolizumab in the first-line induction phase between 01 January 2019 and 01 March 2023. The data of the patients were accessed by entering the hospital information system via computer. Demographic, clinicopathological information, response rates and survival data were recorded retrospectively.

A minimum of 6 cycles of carboplatin (area under the curve 5 mg/mL per min on day 1), etoposide (100 mg/m2 iv on days 1-3) and atezolizumab (1200 mg iv on day 1) were administered in each 21-day cycle of the induction phase. Patients who completed the induction phase received atezolizumab 1200 mg every 3 weeks in the maintenance phase until disease progression or unacceptable side effects according to RECIST criteria or the patients request to discontinue treatment. At the beginning of treatment, all patients underwent positron emission tomography-computed tomography (PET/CT) and cranial magnetic resonance imaging for systemic evaluation of the disease. PET/CT scanning was used to assess response, and thoracic computed tomography (CT) was added when necessary. Response to treatment was evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST version 1.1). Patients who could not be evaluated for response, who received less than 6 cycles of atezolizumab combined with CT in the induction phase, and patients with missing laboratory data were excluded from the study. Treatment-related adverse events were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

Ethics committee approval was obtained from Adnan Menderes University Faculty of Medicine Clinical Research Ethics Committee in accordance with the Declaration of Helsinki (Decision No: 13-2023/93).

Statistical Analysis

Continuous variables were expressed as median (minimum [min] - maximum [max]), categorical variables as frequency and corresponding percentage. Survival data were presented as PFS and OS. Progression-free survival was defined as the time between the start of atezolizumab and first disease progression or death. Overall survival was defined as the time between the initiation of atezolizumab and death or the patient's last hospital visit. Survivals were analysed by the Kaplan-Meier method and the log-rank test was used to investigate the effect of metastasis site on survival. All p values were based on a two-tailed test of significance ($p = 0.05$). Statistical analysis was performed using IBM SPSS version 22 (SPSS Inc, Chicago, Illinois) software.

Results

A total of 24 patients who fulfilled the criteria were included in the study. Twenty patients (83.3%) were male, and the median age was 64 years. Only 8.3% (n:2) of the patients had no smoking history. One third of the patients had no comorbid disease, the most common comorbidities were diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD) and hypertension (HT). All but one patient had small cell neuroendocrine carcinoma. The patient with large cell neuroendocrine carcinoma was treated as SCLC because the Ki67 index was 55%.10 Only 1 patient (4.16%) had recurrent metastatic disease, the other patients had de-novo extensive stage disease. The most common sites of metastasis were lung, bone and non-regional lymph nodes. Five patients had central nervous system (CNS) metastases. Eastern Cooperative Oncology Group (ECOG) performance status was 0 in 45.83% and 1 in 54.16% of patients (Table 1).

In the induction phase, the median number of CT+ atezolizumab cycles was six. Following the induction phase, 70.83% received maintenance therapy and the median number of total atezolizumab cycles was eight. Nine patients (37.5%) died during follow-up. Five patients had brain metastases at diagnosis or during treatment and received cranial radiotherapy (RT). Two patients received prophylactic cranial irradiation (PCI); one received it in the initial limited phase and the other received it during the maintenance phase. A total of 9 patients received consolidative thoracic radiotherapy. One of the patients received thoracic radiotherapy only in the limited phase, while the other eight patients received thoracic radiotherapy in the maintenance phase. The objective response rate (ORR) was 87.5% and 1 patient (4.16%) had progressive disease as the best treatment response. Seven patients had complete response. Thoracal radiotherapy was performed in 71.4% (n:5) of patients with complete response (Table2).

Table 1. Demographic and clinicopathological features of the patients

		Number (n)	% Value
Age, median (min-max) (year)	64 (51-76)		
Gender (male/female)	Male	20	(83.33%)
	Female	4	(16.16%)
Comorbid Disease	DM	8	(33.33%)
	HT	6	(25%)
	CAD	4	(16.16%)
	COPD	7	(29.16%)
	No comorbidity	8	(33.33%)
Smoking Status	Smoker	22	(91.66%)
	Never smoked	2	(8.33%)
ECOG performance status score	0	11	(45.83%)
	1	13	(54.16%)
Histopathology	SCLC	23	(95.83%)
	LCNEC	1	(4.16%)
Stage at the time of diagnosis	Limited	1	(4.16%)
	Extensive	23	(95.83%)
Number of metastatic sites	1	6	(25%)
	2	10	(41.66%)
	3	6	(25%)
	4	0	
		2	(8.33%)

CAD=Coronary artery disease CAD; COPD= chronic obstructive pulmonary disease; DM=Diabetes mellitus; HT=Hypertension; LCNEC= large cell neuroendocrine carcinoma; SCLC= small cell lung cancer

Table 2. Characteristics of therapy and objective tumor responses

		Number (n)	% Value
Patients received cranial irradiation	Yes	7	(29.16%)
	No	17	(70.83%)
Patients received thoracic irradiation	Yes	9	(37.5%)
		15	(62.5%)
CT+Atezolizumab cycles, median (min-max)	6 (6-12)		
Total atezolizumab cycles, median (min-max)	8 (6-54)		
Best response	Complete response	7	(29.16%)
	Partial response	14	(58.33%)
	Stable response	2	(8.33%)
	Progressive disease	1	(4.16%)

At a median median follow-up of 9.4 months (min-max: 5.1-40.4), median PFS and OS were 9.5 months (95% CI: 0.0-25.8) and 30.1 months (95% CI: 3.26-57.004), respectively (Figure 1,2). Analysis using the log-rank test to investigate the effect of the number of metastatic sites on OS showed no significant results (p=0.77) (Figure 3).

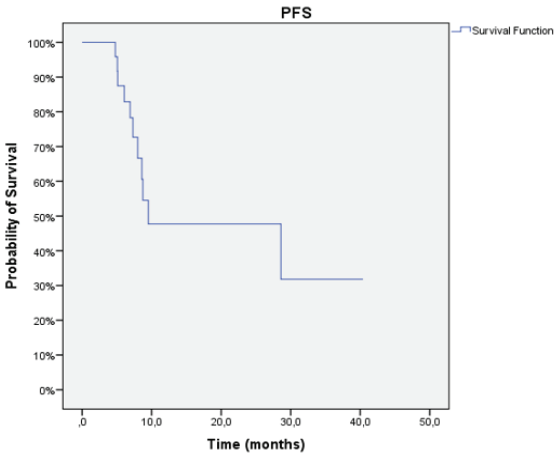

Figure 1. Progression-free survival of the patients

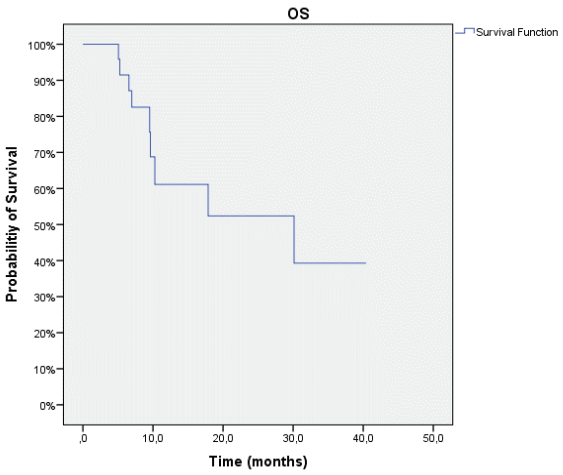

Figure 2. Overall survival of the patients

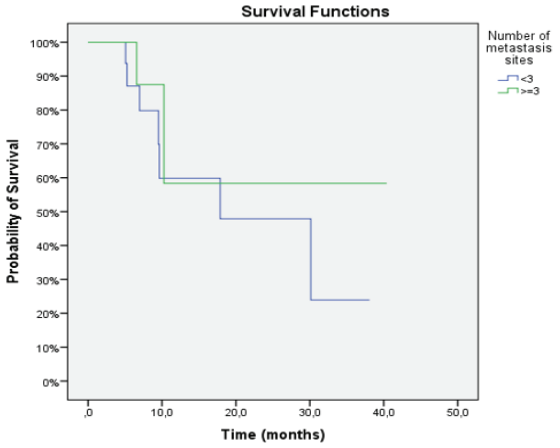

Figure 3. Overall survival by number of metastasis sites > 3, <3

Table 3. Adverse events

Event	Any Grade, n(%)	Grade 1-2, n(%)	Grade 3-4, n(%)
Anemia	19 (79.16%)	12 (50%)	7 (29.16%)
Neutropenia	21 (87.5%)	8 (33.33%)	13 (54.16%)
Thrombocytopenia	13 (54.16%)	9 (37.5%)	4 (16.16%)
Febrile Neutropenia	4 (16.16%)	------	4 (16.16%)
Fatigue	20 (83.33%)	17 (70.83%)	3 (12.5%)
Nausea	12 (50%)	11(45.83%)	1 (4.16%)
Vomiting	8 (33.33%)	8 (33.33%)	-------
Acute kidney injury	3 (12.5%)	3 (12.5%)	--------
Hepatic enzymes elevation	5 (20.83%)	5 (20.83%)	--------
Diarrhea	6 (25%)	6 (25%)	-------
Hypothyroidism	4 (16.16%)	4 (16.16%)	-------
Pneumonitis	1 (4.16%)	1 (4.16%)	-------

Discussion

This retrospective study is the first research that reported the real-life data experience of at least six cycles of CT combined with atezolizumab in the first-line treatment of extensive SCLC in a single center. Patients in our study had the same median age as in IMpower1337, but more patients had an ECOG performance of "0" and the median follow-up was approximately 4 months less. In addition, 25% (37.5% vs. 12.4%) more patients underwent thoracic RT consecutively.

In contrast to the standard median 4 cycles of CT+atzolizumab in the AB.Sahin et al. and IMpower133 studies using real-life data, the median was higher in our study. Similarly, the median number of atezolizumab cycles was similarly higher (8 cycles versus 7 cycles).7,11While the mean ORR in SCLC first-line atezolizumab plus CT studies in this literature was 61%, the ORR in our study was higher at 87.5% (ORR range: 60.2%-63.6%).7,11,12

In our retrospective study, PFS and OS were determined as 9.5 and 30.1 months, respectively. PFS and OS were higher compared to the IMpower133 study, where PFS and OS were 5.2 and 12.3 months, respectively. In another study examining patients with diffuse stage SCLC, median PFS was 6.8 months and median OS was 11.9 months with the combination of atezolizumab and CT.7,12 The most important reason for this may be that there were fewer patients. In addition, in contrast to the previous studies, the inclusion of patients who completed at least 6 cycles of CT+ atezolizumab treatment, the high number of patients with ECOG "0" performance and the fact that we mostly applied thoracic radiotherapy may be factors in the high OS.

In a meta-analysis, age (<65 versus ≥65) and ECOG-PS (0 versus ≥ 1) were found to be associated with response to immunotherapy.13 In our study, the median age of the patients was 64 years and those with ECOG-PS "0" were more common. In addition, giving full dose treatment and tolerating local treatments such as RT in patients with good performance may contribute to a higher OS.

In the phase 3 KEYNOTE-604 study in which pembrolizumab was added to CT in the first-line treatment of extensive stage SCLC, OS was better in patients with ≥3 metastatic sites in the pembrolizumab arm. In our study, no statistically significant relationship was found between the number of metastatic sites and OS. The reason for this may be that our patients were fewer compared to other studies.14

Predictive biomarkers such as PDL-1 expression and tumor mutation burden (TMB) have been investigated to determine the efficacy of immunotherapy treatment in solid tumors such as NSCLC. Although TMB has been shown to be high in SCLC, subgroup analyses of atezolizumab and durvalumab studies have shown that both PD-L1 expression and TMB have no predictive value.15,16 It is known that patients have permanent responses with immunotherapy treatments, and the number of atezolizumab cycles was 12 or more in seven of our patients. Biomarkers that can predict immunotherapy response are important both in delivering treatment to more patients and in applying more aggressive local treatments to patients with response. The need for predictive markers in cancer treatment with immunotherapy, especially progressive SCLC, continues.

In retrospective studies including atezolizumab real-life data, consolidative thoracic RT was applied to an average of 30% patients.11-12 In our study, nine patients (37.5%) received thoracic RT as consolidative treatment. Seven patients received RT in the maintenance phase and one patient received RT before disease recurrence. It has been reported that RT may increase tumor response with direct and abscopal effects in patients receiving immunotherapy treatment.17 Looking at the literature, randomized controlled trials investigating the efficacy and safety of CT plus RT combined with immunotherapy in extensive stage SCLC are lacking.

The overall safety profile in our study was similar to that of the reference studies despite fewer patients. There were no adverse events leading to treatment discontinuation or death. All patients had some degree of adverse events but they were manageable. The most common was bone marrow toxicity. All immune-mediated adverse events were low grade and manageable.

The main limitations of our study are the small number of cases, short follow-up period and retrospective design. In addition, we could not perform further subgroup analyses in patients receiving thoracic radiation. In addition, predictive biomarkers for immunotherapy such as PD-L1 and TMB were not analysed.

Conclusion

In conclusion, these real-life data confirm the efficacy and safety of maintenance atezolizumab with at least six cycles of atezolizumab plus CT in the induction phase in the first-line treatment of extensive SCLC in our small patient series. However, it is crucial to identify predictive biomarkers and clarify the use of thoracic RT. We believe that larger randomised trials with large numbers of patients and real-life data are needed to determine the ideal number of atezolizumab plus CT.

Declaration of Conflicting Interest

Author declares no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Approved by the following research ethics committee

Adnan Menderes University for Non-Invasive Clinical Research (E-53043469-050.04.04-347380, Decision No:13-2023/93).

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Availability of Data and Materi al

The data sets and data analyzed in the study are available from the corresponding author on reasonable request.

Authors Contributions

All authors have made substantial contributions to conception, design, acquisition of data; or analysis and interpretation of data; or have been involved in drafting the manuscript or revising it critically for important intellectual content.

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