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Clinical Outcomes of Chemo-Immunotherapy for Extensive Stage Small Cell Lung Cancer: A Real-World Single Centre Study in Portugal

Resultados do Tratamento com Quimio-Imunoterapia do Cancro do Pulmão de Pequenas Células em Estádio Avançado: Um Estudo Unicêntrico de Vida Real em Portugal

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ABSTRACT

Small cell lung cancer (SCLC) is an aggressive type of lung cancer. Recent studies have provided a new hope by adding atezolizumab to the standard treatment of extensive disease SCLC (E-SCLC). The aim of our study was to evaluate the real-life performance of atezolizumab plus chemotherapy in extensive stage SCLC in a Portuguese setting. Data was collected on twenty patients (70% were male with a mean age of 66.9 years) in treatment at a tertiary hospital in Portugal with E-SCLC treated with chemotherapy and atezolizumab between July 2022 and February 2024. All patients received a carboplatin plus etoposide regimen in combination with atezolizumab. The overall response rate was 55% (95% CI: 31.5 – 76.9) and the disease control rate was 70% (95% CI: 45.7 – 88.1). The median overall survival (OS) and progression-free survival (PFS) was 9.7 (95% CI:5.08 – 14.32) and 7.17 (95% CI:3.28 – 11.05) months, respectively. In total, 13 (65%) patients experienced disease progression and 10 (50%) died during follow-up from events related to the disease. Patients with a performance status score ≥ 2 had lower PFS (p = 0.003) and OS (p = 0.001). To the best of our knowledge, this is the first real-world clinical study in Portugal to evaluate real life outcomes for this combination therapy.

Keywords: Antibodies, Monoclonal, Humanized; Immune Checkpoint Inhibitors; Immunotherapy; Small Cell Lung Carcinoma/drug therapy

RESUMO

O carcinoma pulmonar de pequenas células (CPPC) é um cancro agressivo. Estudos recentes demonstraram benefícios ao adicionar atezolizumab ao tratamento padrão para CPPC em estágio extensivo (CPPC-E). Este estudo avalia o desempenho da combinação de atezolizumab com quimioterapia em contexto de vida real em Portugal. Foram recolhidos dados de vinte doentes (70% homens, com uma idade média de 66,9 anos) com CPPC-E tratados com quimioterapia e atezolizumab num hospital terciário em Portugal, entre julho de 2022 e fevereiro de 2024. Todos receberam carboplatina e etoposido com atezolizumab. A taxa de resposta global foi de 55% (IC 95%: 31,5 – 76,9) e a taxa de controlo da doença foi de 70% (IC 95%: 45,7 – 88,1). A mediana de sobrevivência global (OS) e sobrevivência livre de progressão (PFS) foi de 9,7 meses (IC 95%: 5,08 – 14,32) e 7,17 meses (IC 95%: 3,28 – 11,05), respetivamente. No total, 65% dos doentes apresentaram progressão da doença e 50% faleceram. Doentes com índice de performance (PS) ≥ 2 apresentaram menor PFS (p = 0,003) e OS (p = 0,001). Tanto quanto sabemos, este é o primeiro estudo clínico de vida real em Portugal a avaliar os resultados desta combinação terapêutica.

Palavras-chave: Anticorpos Monoclonais Humanizados; Carcinoma do Pulmão de Pequenas Células/tratamento farmacológico; Imunoterapia; Inibidores de Checkpoint Imunológico

INTRODUCTION

Lung cancer is the leading cause of cancer deaths worldwide and small cell lung cancer (SCLC) is responsible for 15% of cases.[1] Approximately 50% of all SCLC are diagnosed in a metastatic stage with a five-year survival rate below 7%.[1] Despite initial responses to chemotherapy, most patients experience rapid disease progression.[2] The IMpower133 trial has provided new hope by incorporating atezolizumab into the standard treatment of extensive disease SCLC (E-SCLC) alongside chemotherapy.[3]

While clinical trials provide vital data, real-world evidence is essential to assess treatment effectiveness in practical settings. This study evaluated the real-life impact of atezolizumab plus chemotherapy for E-SCLC in a Portuguese setting.

Data was collected on patients with histologically confirmed E-SCLC in follow-up at an oncological pulmonology department in a Portuguese tertiary hospital. The inclusion criteria were age 18 or older, diagnosed with stage III/IV (TNM Classification, 8th edition), had received at least one cycle of chemoimmunotherapy between July 2022 and February 2024, patients could have undergone prior treatments and had measurable disease per the response evaluation criteria in solid tumors (RECIST) version 1.1. Patients with synchronous neoplasia were excluded.

Initial assessments included a thoracic-abdominal-pelvic computed tomography scan (CT), with response evaluations every three cycles. Tumor responses were classified as complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD), and treatment toxicities were assessed according to the common terminology criteria for adverse events (CTCAE) version 5.0.

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Statistical analysis

Progression free survival (PFS) was calculated from the first day of treatment until PD or death from any reason. Overall survival (OS) was calculated from the initiation of treatment until death or was censored on the day of the last visit. The cut-off date was March 31st, 2024. Kaplan-Meier methodology was used to estimate the OS and PFS and the log-rank test was used for survival comparisons. Cox regression was applied to estimate hazard ratios (HRs). All statistical analyses were performed using the IBM® SPSS, version 27.0.

Patients

Characteristics

A total of 20 patients were included. Table 1 shows the patients' characteristics.

Treatment

All patients received a carboplatin/etoposide regimen in combination with atezolizumab. The median number of cycles of chemotherapy plus atezolizumab was 4 (range: 1 – 6) and of maintenance cycles was 2.5 (range: 0 – 19). At data cutoff, 13 (65%) patients had discontinued atezolizumab, due to PD in six (46.2%), death in five (38.5%) and grade ≥ 3 adverse events (AE) in two (15.4%). Second line treatment was initiated in three patients (15%).

Table 1 – Patient characteristics

Characteristics		Patients	PFS		OS	
			Median (95% CI)	***p*-value**	**Median** (95% CI)	***p*-value**
Total patients, n		20				
Age (mean, years)		66,9 ± 7,7				
< 70 years old		15 (75%)	7.2 (4.2 – 11.2)	0.562	6.5 (0.1 – 12.8)	0.463
Elderly (≥ 70 years old)		5 (25%)	5.9 (2.8 – 8.9)		9.7 (6.9 – 12.5)	
Sex						
Female		6 (30%)	7.2 (5.2 – 9.1)	0.828	9.7 (6.9 – 12.5)	0.782
Male		14 (70%)	4.6 (0.196 – 9.1)		6.5 (0.1 – 12.8)	
Smoking status						
Pack-years (mean)		55,5 ± 32,9				
Nonsmokers		1 (5%)	7.2 (3.5 – 10.9)	0.838	7.9 (1.2 – 14.7)	0.640
Ex-smokers/smokers		19 (95%)	7.3 (4.2 – 10.5)		9.7 (3.0 – 16.4)	
ECOG PS						
0 – 1		15 (75%)	7.3 (5.3 – 9.3)	**0.003**	11.3 (7.1 – 15.6)	**0.001**
≥ 2		5 (25%)	2.63 (0 – 6.6)		2.6 (0 – 6.6)	
Comorbidities						
COPD	No	4 (20%)	4.0 (0.2 – 7.8)	0.545	4.0 (0 – 8.3)	0.327
	Yes	16 (80%)	7.2 (5.4 – 8.9)		9.7 (5.8 – 13.6)	
Cardiovascular disease	No	11 (55%)	5.9 (3.6 – 8.2)	0.849	9.7 (3.2 – 16.2)	0.717
	Yes	9 (45%)	7.2 (0.2 – 14.2)		7.9 (0.3 – 15.6)	
Metastasis previous to treatment						
Hepatic metastasis	No	5 (25%)	5.9 (3.2 – 8.6)	0.425	9.7 (2.3 – 17.1)	0.572
	Yes	15 (75%)	7.3 (3.2 – 11.5)		7.9 (3.9 – 12.1)	
Brain metastasis	No	7 (35%)	5.9 (1 – 10.8)	0.365	7.9 (5.0 – 10.9)	0.585
	Yes	13 (65%)	7.2 (2.6 – 11.8)		9.7 (0 – 21.4)	
M1c – Multiple extrathoracic metastasis	No	15 (75%)	5.9 (3.1 – 8.8)	0.655	9.7 (4.1 – 12.1)	0.987
	Yes	5 (25%)	7.3 (4.1 – 10.5)		7.9 (1.6 – 14.3)	
Previous treatment						
Chemo-radiotherapy		11 (55%)	8.6 (3.7 – 13.5)	0.227	7.9 (2.2 – 13.8)	0.203
No		9 (45%)	7.2 (2.9 – 11.5)		11.3 (5.2 – 14.3)	

Treatment related AE were reported in 14 (70%) patients. Grade ≥ 3 events were reported in eight (40%). The most common AE was myelosuppression. Immune-related events were identified in three patients (15%), namely grade 3 colitis, grade 3 uveitis and grade 2 thyroiditis. No patient died of treatment-related AE.

Treatment and survival outcomes

The overall response rate (ORR) was 55% (95% CI:31.5 – 76.9) and the disease control rate (DCR) was 70% (95% CI:45.7 – 88.1). No patient achieved a CR, 11 (55%), three (15%) and six (30%) achieved PR, SD, and PD, respectively.

The median follow-up time was 5.3 months (range: 0.3 – 20.3). The median OS and PFS were 9.7 (95% CI: 5.1 – 14.3) and 7.17 (95% CI: 3.3 – 11.1) months, respectively. In total, 13 (65%) patients experienced PD and 10 (50%) died during follow-up from events related to the disease. Patients with a PS score ≥ 2 had lower PFS and OS than those with a PS score 0 – 1 {p = 0.014 [HR CI 95%: 6.7 (1.6 – 28.2)] and p = 0.006 [HR CI 95%: 10.7 (1.9 – 60.7)], respectively}. Analysis of PFS and OS is shown in Fig. 1 and Table 1.

Atezolizumab plus chemotherapy is the standard of care for extensive stage SCLC since the results of the IMpower133 trial. To our knowledge, this is the first real world clinical study in Portugal to evaluate real life outcomes for this combination therapy. Real-world data differs from clinical trials by including patients with conditions (e.g., higher PS and comorbidities) that often exclude them from trial participation.

This study shows the data of one of the largest pulmonary oncology dedicated departments in Portugal. Comparing data with IMpower133, we found a lower OS (9.7 *vs* 13.2 months) but an improved PFS (7.2 months *vs* 5.2 months).[4] While most real-world studies report PFS

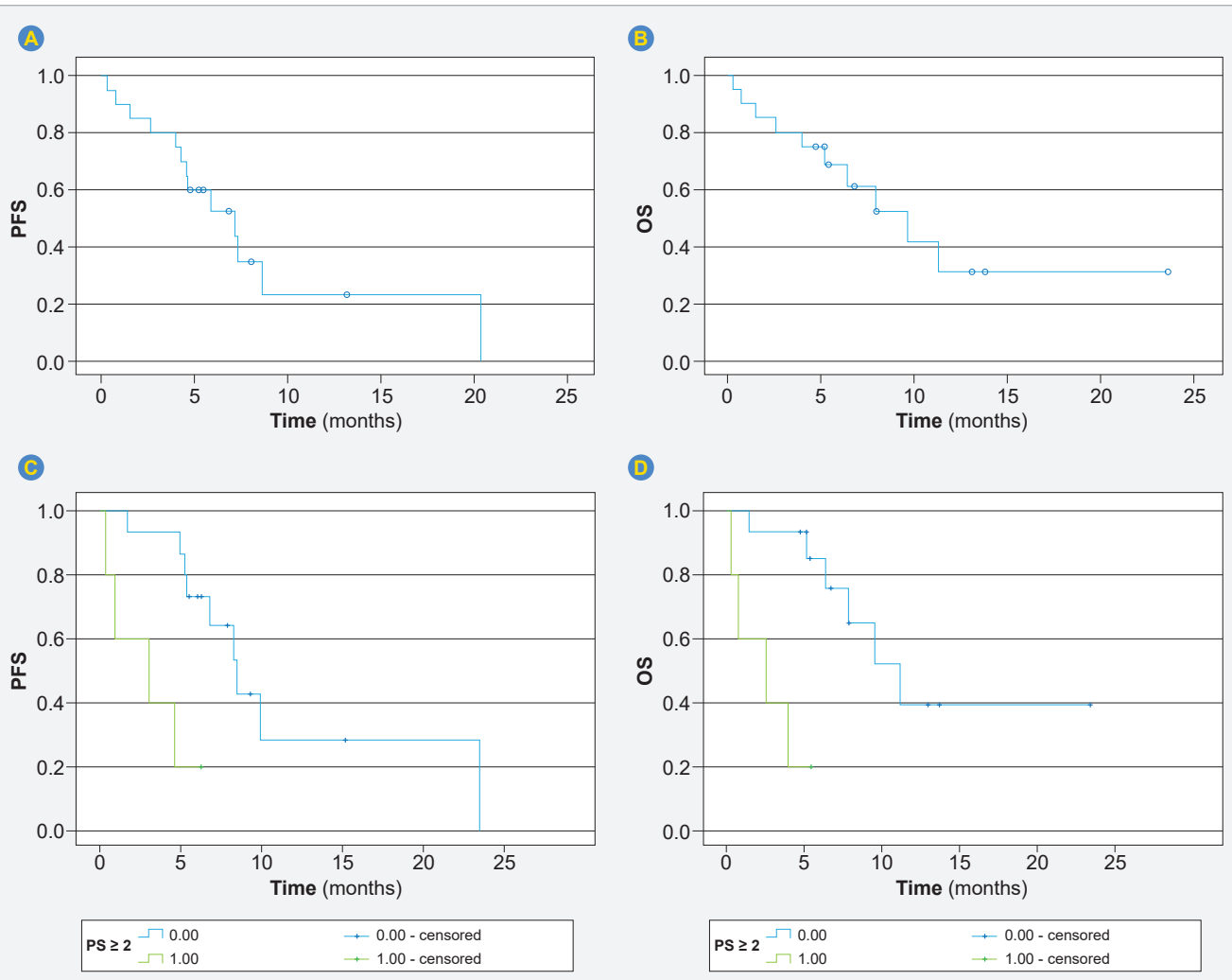

Figure 1 – Kaplan-Meyer analysis of PFS and OS (A and B). Kaplan-Meyer analysis of PFS and OS in patients with PS ≥ 2 (C and D).

comparable to the trial, OS is often higher, contrasting with our findings.[1,5,6] This discrepancy may stem from our inclusion of 25% of patients with PS ≥ 2, compared to fewer than 10% in most studies, thus significantly impacting OS. The higher PFS observed may reflect less strict timing for re-evaluation tests than in the trial. The ORR and DCR were 55% and 70%, respectively, which was similar to the original study as well as most of the real-world studies worldwide.[4-6]

Our study included patients with PS ≥ 2 and elderly patients. We found that patients with PS ≥ 2 had significantly lower OS and PFS, consistent with other studies suggesting immunotherapy benefits patients with lower PS scores.[1,5,7] Contradictory results can be found in the literature regarding older age.[1,4,5,8] In our study, older age was not associated with a difference in response rate or survival.

Comorbidities may influence SCLC outcomes significantly. Cardiovascular disease was associated with lower survival in a recent study.[7,9] We found no difference in OS or PFS in patients with cardiovascular disease.

In line with the original study, chemoimmunotherapy was safe and well tolerated. The most common AE were related to chemotherapy.[4] Immune-related toxicity occurred in 15% of patients, which was lower than the 39.9% observed in IMpower133 (39.9%).[4]

Considering the findings in this small, but relevant study, it is safe to say that chemoimmunotherapy combination is a safe option for patients with E-SCLC and its effect estimates are comparable to those in the IMpower133 trial in the Portuguese population. It is of extreme importance to identify which patients benefit more from this therapy.

Study limitations include its retrospective design, potential patient evaluation bias, and small sample size. Future multicenter studies are needed to further evaluate real-life outcomes.

AUTHOR CONTRIBUTIONS

DN: Data collection, writing of the manuscript.

MB, ASV, FF, ALM, DH, PV: Writing and critical review of the manuscript.

All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in October 2024.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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