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Brief Report of the use of Atezolizumab Plus Chemotherapy in Patients with Advanced Small-Cell Lung Cancer: A Real-World Data

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1. Abstract

Background: Lung cancer causes the greatest number of cancer deaths worldwide in both sexes. Around 2.2 million new diagnosis and 1.8 million deaths were estimated in 2020. Small-cell lung cancer represent only the 15 % of all cases. Currently, the combination of chemo-immunotherapy has been constituted as a new standard of care for the first-line treatment of metastatic disease. Material and methods: This is an observational, retrospective study at a single healthcare institution (MD Anderson Cancer Center Madrid), which included patients diagnosed and treated for small cell lung carcinoma between September 2018 and July 2023, treated in 1L with double-platinum based chemotherapy plus atezolizumab. Results: A total of 22 patients diagnosed with SCLC between September 2018 and August 2022 were included. The average age was 68 years (range 51.7 to 84.5), 82 % were men. The median duration of the 1L was 14 months (range 12.8-58.6 months), with the median overall survival of 16 months (range 2.5-49 months). The percentage the objectives responses was 72.5 %. In 41 % of the patients no relevant adverse events were described. Conclusion: This study provides an updated overview of the clinical situation and the improve in survival of patients with SCLC treated in 1L with chemotherapy plus atezolizumab in the current clinical practice.

2. Introduction

Lung cancer causes the greatest number of cancer deaths worldwide in both sexes. Around 2.2 million new diagnosis and 1.8 million deaths were estimated in 2020 [1]. According to the histologic type we can recognize two groups: the non-small cell lung cancer (NSCLC) that represents the majority of diagnosed lung cancer cases (80%) and the small-cell lung cancer (SCLC), which occurs in approximately 15 % of patients [2]. SCLC have a strong epidemiological link to tobacco and only less than 2 % of cases appear in never-smokers [3]. Other factors such as the asbestos exposure, radiation, radon gas and the environmental pollution have been also associated with the disease [4].

The SCLC has an exceptionally high mortality rate relative to other solid tumours, with a 5-year survival rate of below 7 % [5]. This type of tumor is characterized by a rapid growing, early development of metastases, and endocrine paraneoplastic syndromes and this is the reason why patients develop symptoms quickly [4-5]. Usually, to choose the type of treatment, the disease is defined as a limited stage (only thoracic disease or LS-SCLC) or an extended stage (distant metastasis or ES-SCLC). In both cases, chemotherapy (CT) based on a platinum-doublet (cisplatin or carboplatin) is the basic pillar of treatment and the use of etoposide is recommended. In patients with LS-SCLC the thoracic radiation therapy (RT) along with CT is also recommended to improve local control and survival, following the prophylactic cranial irradiation (PCI) [6]. Currently, the combination of chemo-immunotherapy has been constituted as a new standard of care for the first-line (1L) treatment of metastatic disease. This is the most remarkable

hallmark of progress in the treatment of the metastatic disease [7-9]. We have conducted a retrospective study and we present a descriptive analysis of the ES-SCLC population treated in 1L with atezolizumab plus CT in a single institution.

3. Material and Methods

This is an observational, retrospective study at a single healthcare institution (MD Anderson Cancer Center Madrid), which included patients diagnosed and treated for small cell lung carcinoma between September 2018 and July 2023, treated in 1L with double-platinum based chemotherapy plus atezolizumab. The protocol was approved by the Ramón y Cajál Hospital Ethics Committee and was conducted in accordance with the precepts of the Code of Ethics of The World Medical Association (Declaration of Helsinki). Data were collected by research teams from patient medical records using an electronic data capture system and were included in a RedCap database. The characteristics collected included: sociodemographic, epidemiological, clinical (smoking history, histological subtype, TNM Classification of Malignant Tumours -8th Edition-, and location of metastases), treatment patterns (CT, IO, RT), response and survival. The variables are described as frequencies in the entire population and percentages. All analyses were performed using Stata v14.1 (StataCorp, 2015, College Station, TX).

4. Results

A total of 22 patients diagnosed with SCLC between September 2018 and August 2022 were included. The average age was 68 years (range 51.7 to 84.5). There were 4 women (18 %) and 18 men (82 %). The rest of the clinical characteristics are described in (Table 1).

All the patients were treated in the 1L of metastatic disease with platinum-doublet plus atezolizumab. Of the 22 patients, 19 (86.4 %) were treated with carboplatin/etoposide plus atezolizumab, 2 of them (10 %) with cisplatin/etoposide plus atezolizumab, and one patient (4.6 %) with carboplatin/paclitaxel plus atezolizumab. The median duration of the 1L was 14 months (range 12.8-58.6 months), with the median overall survival (OS) of 16 months (range 2.5-49 months) (Figure 1).

Eight patients (36 %) received consolidation chest radiotherapy treatment, 4 (18 %) prophylactic cranial irradiation (PCI), and 8 (36 %) received palliative RT at some moment of the evolution of the disease. The distribution according to the types of responses was the following: 4 complete responses (18 %), 12 partial responses (54.5 %), 3 stable disease (14 %), 2 progression disease (9 %), and one case that was not valuable.

Of all 22 patients included in the study at the moment of the disease progression, 7 received 2L treatment, 5 received 3L treatment, and only 2 received 4L treatment. In all cases patients received CT (Table 2). Response rates to 2L and subsequent lines were insignificant, reaching a maximum of stable disease with a median duration of response of 4.8 months (range 1.1-10 months) in 2L.

The tolerability profile was good with a total of 9 patients (41 %) in whom no relevant adverse events were described. Any new toxicity was not described in previous publications and those presented are described in (Table 3). Fifty-four percent of the adverse events were mild (grade 1-2), 31 % grade 3 (corresponding to afebrile neutropenia) and 2 patients (15.4 %) with grade 4 events (one febrile neutropenia and one pneumonitis), without any fatal case.

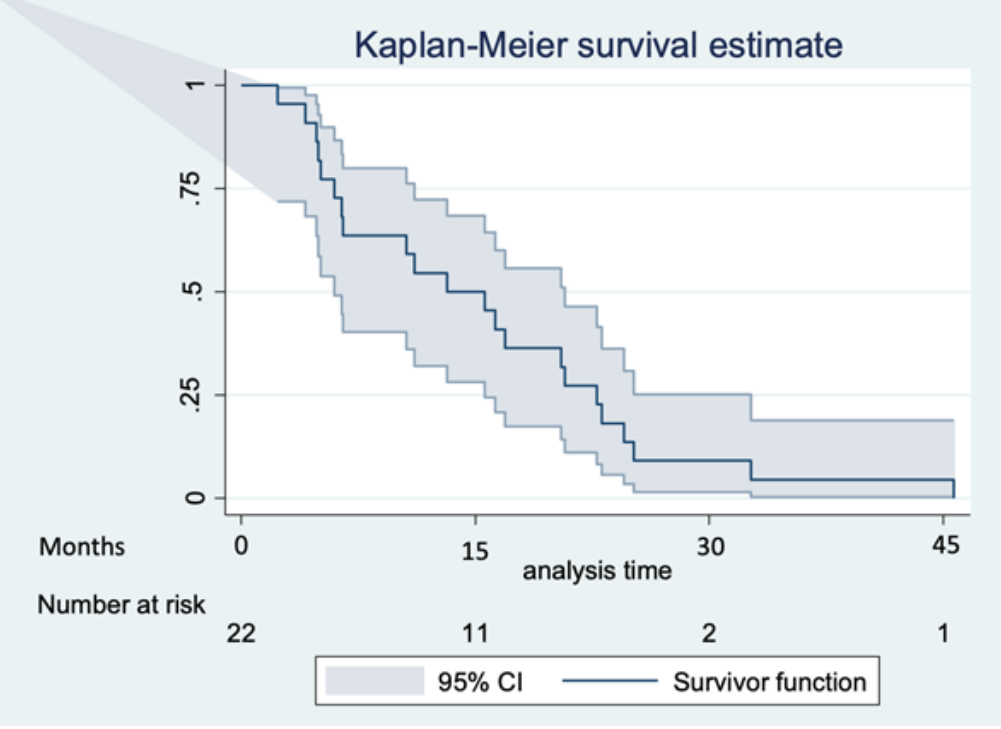

Figure 1: Overall survival in patients treated in first-line with platinum-doublet plus atezolizumab.

Table 1: Clinical characteristics of patients with small-cell lung carcinoma

Characteristics	Number (%)
Sex	
Man	18 (82 %)
Woman	4 (18 %)
Average age	68 years (range 51.7-84.5)
Smoking habit	22 (100 %)
Tumor	
T1	1 (4.5 %)
T2	6 (27.2 %)
T3	7 (32 %)
T4	8 (36.3 %)
Lymph nodes	
N0	3 (13.8 %)
N1	6 (27.2 %)
N2	4 (18 %)
N3	9 (41 %)
Metastasis	
M0	4 (18 %)
M1	18 (82 %)
Initial stage	
IIIA	3 (13.5 %)
IIIC	1 (4.5 %)
IVA	2 (9.0 %)
IVB	16 (73 %)
Location of metastatic disease	
Pleural / pulmonary	5 (23 %)
Bone	9 (41 %)
Liver	8 (36 %)
Central nervous system	11 (50 %)
Distant lymph nodes	4 (18 %)
Adrenal	3 (14 %)

Table 2: Description of subsequent treatment after the failed to atezolizumab plus chemotherapy

	2L (nº)	3L (nº)
Carboplatin / paclitaxel	5	1
Irinotecan	2	1
Lurbidectedin	0	1
Topotecan	0	1
Paclitaxel	0	1

Table 3: Description and frequency of adverse events in patients treated with atezolizumab plus chemotherapy

Adverse event	Number	Percentage
Febrile neutropenia	1	4.5 %
Afebrile neutropenia	4	18 %
Pneumonitis	1	4.5 %
Thyroiditis	3	14 %
Bicytopenia	1	4.5 %
Skin rash	1	4.5 %
Peripheral neuropathy	1	4.5 %

5. Discussion

The addition of checkpoint inhibitors (ICI) to platinum doublet-based CT treatment has resulted in improved disease control and survival rates [6, 9]. Several phase III clinical trials confirm this benefit and the safety of these drugs in this pathology with few therapeutic options, particularly the combinations of CT plus Atezolizumab and Durvalumab. IMpower133 enrolled more than 400 patients with ES-SCLC who had received no prior CT for metastatic disease and had a good performance status. Patients were randomized 1:1 to receive atezolizumab plus carboplatin and etoposide every 3 weeks for a maximum of 4 cycles, followed by atezolizumab every 3 weeks until disease progression or unacceptable toxicity or the same scheme of CT plus placebo for a maximum of 4 cycles, followed by placebo every 3 weeks until disease progression or unacceptable toxicity [7]. The updated analysis with a median follow-up for OS of 22.9 months, confirmed the superiority of the combinate treatment (CT plus Atezolizumab) vs CT alone showing a median OS of 12.3 and 10.3 months, respectively (hazard ratio, 0.76; 95% CI, 0.60 to 0.95; P = 0.0154). The efficacy of the addition of atezolizumab to CT, regardless the PD-L1 expression by immunohistochemistry or the tumoral mutational burden (TMB) status was demonstrated [10]. Recently, in September 2023 during the IASLC World Conference on Lung Cancer (WCLC) the results of Phase IV IMbrella A an open-label, non-randomised, multicentre extension and long-term observational study have been presented. A total of 18 patients, treated in the experimental arm in the IMpower133, were enrolled and a long term analysis (median follow-up was 59.4 months) showed a 5-year OS rate of 12%. Only 3 serious adverse events (AEs) have been reported and included diarrhea, pneumonia, and procedural pneumothorax. At the moment of the analysis 11 patients stay alive 5 years later. These data showed a long-term safety profile of atezolizumab plus carboplatin / etoposide and the late onset immune-related toxicities were rare and manageable [11].

In this observational and retrospective study, we analyzed a series of 22 patients, diagnosed with SCLC between September 2018 and August 2022 and treated in 1L with doublet platinum CT plus atezolizumab. The data represent the efficacy of this scheme of treatment in the real clinical practice in a single institution. The baseline characteristics of patients are similar to the IMpower133 population with an average age of 68 years (range 51.7 to 84.5), 82 % of them- men [7]. Nineteen patients (86.4 %) were treated with carboplatin/etoposide plus atezolizumab, 2 of them (10 %) with cisplatin/etoposide plus atezolizumab, and one patient (4.6 %) with carboplatin/paclitaxel plus atezolizumab. The median duration of the 1L was 14 months (range 12.8-58.6 months), the median OS was 16 months (range 2.5-49 months). The tolerability profile was good, no new toxicity was described and the major of AEs were mild (54 %) without any fatal case. These results are consistent with previously published efficacy and safety results [7, 12-13].

Several analyzes on efficacy and safety in patients, treated with the combination of atezolizumab with carboplatin/etoposide, have been performed. All of these studies are consistent in demonstrating that in the context of ES-SCLC, the treatment with atezolizumab plus CT followed by maintenance with atezolizumab contributes to improve the OS with a very good safety profile. An exploratory analysis evaluates the benefit of the maintenance therapy compared with placebo in this context and the results show a superior median OS in the experimental arm with 12.5 vs 8.4 months (HR = 0.59, 95% CI: 0.43-0.80). The rate of the related AEs since the beginning of the maintenance therapy was 41 % vs 25 % and the grade 3 or 4 toxicity was 28 % vs 23 %, without any fatal event in the atezolizumab arm [12].

All data and medical recommendations indicate that currently the best treatment option for patients with ES-SCLC is the combination of CT plus ICI. These data are more favorable for combinations of platinum doublet plus atezolizumab or durvalumab (phase III trials) [14]. Although our study is limited by the retrospective nature of this analysis, our strength includes the real-world cohort. The efficacy data from randomized clinical trials are reproducible in our clinical practice in a pathology as complete as SCLC and improves the survival and the quality of life of the patients. According to our results we consider that the combination of CT plus ICI is an optimal first line of treatment for ES-SCLC as other real-world studies have proved it [15].

In conclusion, in our real-world ES-SCLC population, treated with the combination of atezolizumab plus carboplatin/etoposide followed by atezolizumab maintenance, the efficacy and the safety of this regimen has been demonstrated. We believe that the combination of chemotherapy plus immunotherapy in these patients is the first-line treatment of choice, if there are no contraindications for it.

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