Research Paper

Real-World Effectiveness and Safety Profile of Atezolizumab in Small-Cell Lung Cancer Treatment

ROBERTO LOZANO*, MARIA ESTHER FRANCO AND CARINA BONA1

Department of Pharmacy, University Clinical Hospital "Lozano Blesa", [1]Unit for the Rational Use of Medicines, Aragon Health Service, Zaragoza 50009, Spain

Atezolizumab, a programmed death ligand 1 inhibitor, has shown improved survival outcomes in extensive-stage small-cell lung cancer when combined with chemotherapy. However, its real-world effectiveness and safety profile require further evaluation. This retrospective study examines demographic characteristics, treatment responses, and adverse effects in 135 patients treated with Atezolizumab in Aragon, Spain. Treatment discontinuation was primarily due to disease progression (40 %) and toxicity (15 %). The most common immune-related adverse events included pneumonitis and hepatitis. Statistical tests identified a significant association between cumulative Atezolizumab exposure and the occurrence of pneumonitis and hepatitis, suggesting that the dose of treatment could be an important risk factor for these adverse effects. These findings highlight the importance of enhanced toxicity monitoring and personalized treatment strategies. Clinicians should carefully assess the risk of immune-related adverse events, particularly in patients receiving higher doses of Atezolizumab.

Key words: Atezolizumab, cancer, lung, side effects

Lung cancer continues to be one of the leading causes of cancer-related mortality worldwide, with Small-Cell Lung Cancer (SCLC) accounting for approximately 15 % of all lung cancer cases[1]. SCLC is a highly aggressive malignancy characterized by rapid tumour proliferation, early metastatic spread, and a limited range of treatment options, which ultimately leads to a poor prognosis. For years, the standard first-line treatment for Extensive-Stage SCLC (ES-SCLC) has been platinum-based chemotherapy, which, although effective to some extent, only provides modest improvements in overall survival. This has driven the search for more effective treatments.

Recent advances in the field of immunotherapy have transformed the therapeutic landscape for SCLC. The integration of Immune Checkpoint Inhibitors (ICIs), such as Atezolizumab, has shown promising potential in improving survival outcomes in SCLC patients. Atezolizumab, a monoclonal antibody that targets Programmed Death Ligand 1 (PD-L1), works by enhancing anti-tumour immune responses, primarily through the restoration of T-cell activity. The landmark IMpower133 trial demonstrated that adding Atezolizumab to the chemotherapy combination of carboplatin and etoposide significantly improved overall survival in patients with ES-SCLC, resulting in the Food and Drug Administration (FDA) approval of Atezolizumab as a first-line treatment[2].

Despite the clinical efficacy of Atezolizumab and other ICIs, their use is associated with a range of immune-related Adverse Events (irAEs) that can affect multiple organ systems. These adverse effects often require treatment modifications, including discontinuation of therapy and, in some cases, the use of immunosuppressive therapies[3]. These side effects pose significant challenges in managing patients and optimizing treatment outcomes.

While clinical trials have demonstrated the benefits of Atezolizumab, there is a lack of comprehensive real-world evidence regarding its effectiveness and safety profile outside controlled settings. Understanding

***Address for correspondence**
E-mail: rlozano@salud.aragon.es

Accepted 16 June 2025
Revised 22 March 2025
Received 21 March 2025
Indian J Pharm Sci 2025;87(3):108-113

how patient characteristics, treatment responses, and adverse effects manifest in everyday clinical practice is essential for making informed decisions about treatment selection and managing associated toxicities. This study aims to provide valuable insights into the demographic profile, treatment responses, and incidence of adverse events among patients treated with Atezolizumab. Furthermore, it seeks to identify risk factors for treatment-related toxicity, which will contribute to the development of personalized treatment strategies for SCLC patients, ultimately enhancing treatment outcomes and improving patient safety[4].

MATERIALS AND METHODS

This study was conducted as a retrospective observational cohort analysis in hospitals across Aragón, Spain, focusing on patients with SCLC who received Atezolizumab-based therapy between 2021 and 2024. The primary objective was to assess the demographic characteristics, treatment responses, and the incidence of irAEs in these patients. The study utilized anonymized electronic hospital records in strict adherence to data protection regulations and ethical guidelines to ensure patient confidentiality.

Study population:

The study population consisted of patients with histologically confirmed SCLC who had initiated treatment with Atezolizumab in combination with platinum-based chemotherapy. Patients were included if follow-up data regarding treatment response and adverse effects were available, allowing for a comprehensive evaluation of clinical outcomes. This approach ensured that only patients with sufficient follow-up data were included, which was essential for evaluating both the effectiveness and safety of the treatment.

Data collection:

A wide range of demographic, clinical, treatment-related, and safety-related parameters were collected to provide a thorough assessment of the patients and their responses to treatment. The following variables were recorded:

Demographic variables: These included age, sex, and geographic origin.

Clinical parameters: These included Eastern Cooperative Oncology Group (ECOG) performance status (categorized as low (0-1) or high (≥2)), the presence of active or corticosteroid-dependent brain metastases, and the adequacy of hematological and organ function.

Prior treatments: The study also recorded whether patients had received any prior treatments for SCLC to account for pre-existing therapeutic exposure.

Treatment-related variables:

The treatment-related data collected included:

Total dose of Atezolizumab administered throughout the treatment period.

Treatment discontinuation: Whether the patient discontinued treatment, along with the specific reason for discontinuation, which could be due to disease progression, toxicity, mortality, or other factors.

Primary outcome:

The primary outcome of interest was the incidence of irAEs, which were classified based on the organ systems affected. These were grouped as follows:

Respiratory toxicities: Pneumonitis

Hepatic toxicities: Hepatitis

Gastrointestinal complications: Colitis

Neurological complications: Hypophysitis, myasthenic syndrome, guillain-barré syndrome, and meningoencephalitis.

Other immune-mediated toxicities: Type 1 diabetes mellitus, pancreatitis, myocarditis, myositis, and nephritis

Exploratory analysis of risk factors and causes of treatment suspension:

An exploratory analysis was conducted to investigate risk factors and causes of treatment suspension and/or side effects (such as pneumonitis, hepatitis, colitis, hypothyroidism, and others) in patients with SCLC treated with Atezolizumab. The factors considered included:

Demographic variables: Age and sex.

Clinical factors: Prior treatment history, histological confirmation of SCLC-ES, presence of measurable disease according to Response Evaluation Criteria in Solid Tumours (RECIST) criteria, ECOG, brain metastases, and hematological and organ function adequacy.

Treatment factors: Total dose of Atezolizumab administered and reasons for treatment suspension (e.g., disease progression, toxicity, mortality).

Statistical analysis:

To evaluate associations between categorical variables (e.g., sex, previous treatment history, presence of metastases) and the cause of treatment suspension and/or side effects, Fisher's exact test was performed. For continuous variables (such as age and total dose administered), the Mann-Whitney U test was used to assess differences between patients who suspended treatment due to disease progression and those who suspended for other reasons. All statistical tests were performed with a significance level set at $p<0.05$.

Ethical considerations:

This study was conducted in accordance with the ethical principles governing biomedical research involving human data. Since the research utilized de-identified secondary data from electronic hospital records and did not involve direct patient intervention, formal ethical approval was not required based on institutional guidelines. However, all research activities adhered to international ethical standards, including those outlined in the Declaration of Helsinki, as revised in 2000, ensuring the protection of patient rights and data confidentiality throughout the study.

RESULTS AND DISCUSSION

The analysis included 135 patients with SCLC who were treated with Atezolizumab. The sample was predominantly male (69.6 %), with a mean age of 66 y (range: 41 y to 86 y). The primary cause for treatment discontinuation was disease progression, which accounted for 89.9 % of cases, followed by other reasons such as unmanageable toxicity and death (10.1 %).

Demographic and clinical characteristics, treatment response, and treatment discontinuation among the 135 patients treated with Atezolizumab, 70 % were male (n=94) and 30 % were female (n=41). The average age of the cohort was 66.1 y (±8.6). Histological confirmation of SCLC was obtained in 90 % of cases (n=122), either through histology or cytology. Brain metastases were present in 4 % (n=6) of the patients. The ECOG performance score had a median value of 0.62 (±0.49), suggesting that most patients had a relatively good functional status at the initiation of treatment.

Patients in this cohort received an average of 8.4 g (±7.6) of Atezolizumab. The majority of patients, 91 % (n=123), had measurable disease according to RECIST 1.1 criteria. Prior to receiving Atezolizumab, 90 % (n=121) of patients were treatment-naive, meaning they had not previously undergone any treatment for their condition.

Survival data revealed that 20.7 % (n=28) of patients survived for 10 mo or less, while 1.5 % (n=2) survived for 18 mo or more. Disease progression was the primary reason for treatment discontinuation, accounting for 24 % (n=33) of cases. Toxicity-related discontinuation occurred in 1.5 % (n=2) of patients, while mortality accounted for 7.4 % (n=10) of treatment suspensions.

Fisher's exact test was used to evaluate the relationship between categorical variables (e.g., sex, previous treatment history, presence of metastases) and the cause of treatment suspension. The results indicated no significant associations between categorical variables and treatment suspension causes, as all p-values were greater than 0.05 as shown in Table 1.

For the continuous variables (age and number of vials administered), the Mann-Whitney U Test was employed to compare the distributions between patients who suspended treatment due to disease progression and those who discontinued for other reasons.

The p-value of 0.3112 for age indicates no significant difference in the ages of patients who discontinued treatment due to disease progression vs. those who suspended treatment for other reasons.

The p-value of 0.0500 for the total dose administered suggests a marginally significant difference, indicating that the total dose of Atezolizumab may influence the likelihood of treatment suspension as shown in Table 2.

TABLE 1: RISK VARIABLES AND THE CAUSE OF TREATMENT SUSPENSION

Categorical variable	P valué
Sex	1.0
Previous treatment for SCLC-ES	0.0966
Présense of brain metastases	0.1904
Adequate hematological and organ function	1.0
SCLC-ES confirmed histologically or cytologically	1.0

TABLE 2: FOR THE CONTINUOUS VARIABLES AGE AND NUMBER OF VIALS ADMINISTERED

Continuous variable	P value
Age	0.3112
Total dose of Atezolizumab administered	0.0500

In the analysis of side effects, several irAEs were analysed, including pneumonitis, hepatitis, colitis, hypophysis's, type I diabetes, severe skin reactions, myasthenia syndrome/myasthenia gravis, Guillain-Barré syndrome, meningoencephalitis, pancreatitis, myocarditis, myositis, and nephritis. Due to the absence and/or low frequency of certain side effects, such as pneumonitis (n=1, 0.7 %) and hepatitis (n=2, 1.4 %), these were grouped together into a broader category labelled "other side effects". This approach allowed for a more comprehensive analysis of the data.

Fisher's Exact Test was conducted for categorical variables to assess the association between demographic and clinical characteristics (e.g., sex, previous treatment history, presence of brain metastases) and the newly combined "other side effects" category.

Sex (p=1.0), previous treatment (p=0.2135), and presence of brain metastases (p=1.0) showed no significant association with the occurrence of other side effects.

Adequate hematological and organ function (p=0.0566) showed a marginally significant association, suggesting that patients with adequate organ function may have a slightly higher likelihood of experiencing side effects, though this requires further investigation with a larger sample as shown in Table 3.

For continuous variables, the Mann-Whitney U Test was used to compare the distribution of age and number of vials administered between patients who experienced other side effects and those who did not.

Age (p=0.2473) showed no significant difference in the occurrence of other side effects, suggesting that age is not a significant factor in side effect development in this dataset.

Total dose administered (p=0.0261) showed a statistically significant difference, indicating that patients who received more vials of Atezolizumab were more likely to experience other side effects as shown in Table 4.

The demographic characteristics of patients with SCLC treated with Atezolizumab in Aragón align with findings from previous studies, highlighting a predominance of older males[1]. In this study, the majority of patients exhibited a preserved functional status (ECOG 0-1) at the time of treatment initiation, which is consistent with the feasibility of administering immunotherapy to relatively fit populations. This is important because it suggests that immunotherapy, particularly with agents like Atezolizumab, can be effectively utilized even in patients who are not severely debilitated at the start of treatment[5]. Despite its well-established efficacy, this study underscores the critical challenges that still exist, particularly in relation to treatment discontinuation, which was primarily caused by disease progression and irAEs[2].

The analysis did not reveal a significant association between age and the cause of treatment suspension among patients with SCLC treated with Atezolizumab. Specifically, the Mann-Whitney U Test for age showed no significant differences between patients who suspended treatment due to disease progression and those who did so for other reasons (p=0.3112). This suggests that age does not appear to significantly influence treatment suspension decisions within this cohort, implying that factors other than age may be more influential in determining whether treatment is discontinued.

However, the analysis of treatment dose revealed a marginally significant association (p=0.0500), suggesting that the total dose of Atezolizumab administered may influence the likelihood of treatment suspension. Patients who received higher doses or a longer duration of treatment were somewhat more likely to experience treatment discontinuation, primarily due to disease progression or other treatment-related factors. This finding highlights the importance of monitoring cumulative treatment doses closely, as the likelihood of suspension might be dose-dependent[5]. Future studies, particularly those involving larger sample sizes, would be beneficial in further validating these results and exploring whether a threshold exists beyond which the risk of treatment discontinuation increases significantly. These results underscore the importance of dose management and toxicity monitoring in patients receiving Atezolizumab.

While age did not significantly influence treatment suspension, clinicians should focus on monitoring patients for signs of treatment intolerance, especially those receiving higher doses. Further prospective studies with larger cohorts and more detailed data on treatment responses and toxicity are necessary to confirm these findings and optimize treatment strategies [3].

To explore potential risk factors for side effects, this study combined rare adverse effects, such as Pneumonitis and Hepatitis, into an "other side effects" category due to their low occurrence in the dataset. The analysis showed that age was not a significant factor influencing the occurrence of these side effects. This aligns with previous studies that suggest age may not be a strong predictor of immune-related adverse effects in patients undergoing immunotherapy[3]. However, the total dose administered of Atezolizumab was found to have a statistically significant association with the occurrence of other side effects (p=0.0261). This suggests that higher doses of Atezolizumab may increase the likelihood of developing immune-related adverse effects, highlighting the need for careful monitoring of patients who receive higher treatment doses[4].

Interestingly, while the Fisher's Exact Test showed no significant associations for sex or previous treatment history, a marginally significant association was observed with adequate hematological and organ function (p=0.0566). This finding suggests that patients with better baseline organ function might be slightly more likely to experience side effects, though further research with larger sample sizes is needed to confirm this association. The potential link between organ function and side effect susceptibility warrants additional investigation, as it may help refine patient selection criteria and optimize treatment planning.

A key strength of this study is its real-world analysis of Atezolizumab in SCLC patients, providing valuable clinical data that complement findings from controlled trials. Detailed patient records enabled a comprehensive evaluation of treatment-related adverse effects, enhancing understanding of dose-dependent immune-related toxicities, which can inform future treatment strategies.

However, the study has several limitations. Its retrospective nature may introduce selection bias and limit causal inferences between treatment exposure and adverse events. The small sample size (135 patients) may reduce statistical power and limit the generalizability of the results. Additionally, the lack of long-term follow-up data restricts conclusions on the durability of treatment effects and late-onset toxicities.

Other limitations include the categorization of side effects into an "other side effects" group, which may have introduced heterogeneity. The grouping of age into broad categories could have masked subtle differences. Moreover, the absence of detailed data on the severity and timing of side effects limits the depth of the analysis. Future studies with larger sample sizes, detailed longitudinal data, and refined side effect classifications are needed to confirm these findings.

Overall, the findings suggest that the total dose administered of Atezolizumab may play a significant role in the likelihood of developing irAEs. Clinicians should carefully monitor patients who receive higher doses of Atezolizumab for the potential development of side effects, especially those related to immune system activation. Additionally, patient characteristics, such as organ function and previous treatment history, could help predict which individuals are more likely to experience these adverse reactions.

TABLE 3: ASSOCIATIONS BETWEEN RISK VARIABLES AND SIDE EFFECTS

Categorical Variable	p-value (Other side effects)
Sex	1.0
Previous treatment for SCLC-ES	0.2135
Presence of brain metastases	1.0
Adequate hematological and organ function	0.0566
SCLC-ES confirmed histologically or cytologically	Not valid

TABLE 4: FOR CONTINUOUS VARIABLES, THE MANN-WHITNEY U TEST

Continuous Variable	p-value (Other side effects)
Age	0.2473
Total dose of Atezolizumab administered	0.0261

Ethical approval:

Also, authors declare that this paper has not been submitted elsewhere in similar form, and all authors have contributed significantly to the publication and are aware of the submission and agree with it.

Funding:

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interests:

The authors declared no conflict of interests.

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