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Clinical outcomes of concurrent use of corticosteroids and immune checkpoint inhibitors in oncology

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Immunotherapy has transformed metastatic non-small cell lung cancer (mNSCLC) treatment. Immune checkpoint inhibitors (ICIs) enhance antitumor immunity, but systemic corticosteroids may counteract their effects. While systemic corticosteroids are known to impair ICI outcomes, the impact of inhaled corticosteroids remains unclear. This study assessed the influence of systemic corticosteroids and inhaled corticosteroids on ICI efficacy in mNSCLC patients. This single-center cohort study included 105 mNSCLC patients receiving pembrolizumab or atezolizumab (2016–2024). Patients were classified into three groups: (1) no corticosteroids, (2) systemic corticosteroids use (≥10 mg prednisolone-equivalent), and (3) inhaled corticosteroids use. Clinical outcomes included objective response rate, disease control rate, progression-free survival, and overall survival. Kaplan-Meier analysis and Cox regression evaluated corticosteroid impact. Analyses were conducted using Stata 18.0. Among the 105 patients, 38 received systemic corticosteroids (SCS), 16 received inhaled corticosteroids (ICS), and 51 did not receive corticosteroids. ICS use was associated with chronic obstructive pulmonary disease, while SCS use was more frequent in older patients. Patients receiving systemic corticosteroids exhibited significantly worse progression-free survival (4.1 vs. 8.6 months in the non-steroid group) and overall survival (6.9 vs. 20.1 months). Inhaled corticosteroid use did not negatively impact survival (median overall survival: 35.1 months). Multivariate analysis identified systemic corticosteroid use and cardiovascular disease as independent predictors of poor prognosis, while chronic obstructive pulmonary disease was associated with improved outcomes. Notably, long-acting systemic corticosteroids (dexamethasone) were linked to worse survival than intermediate-acting systemic corticosteroids (4.7 vs. 9.7 months). In conclusion, systemic corticosteroids, especially long-acting forms, significantly reduce ICI efficacy and predict worse survival in mNSCLC. Conversely, inhaled corticosteroid use does not impair treatment outcomes. Chronic obstructive pulmonary disease may be a favorable prognostic factor for immunotherapy response. These findings highlight the importance of cautious corticosteroid use in optimizing ICI therapy.

Keywords: systemic corticosteroids; inhaled corticosteroids; non-small cell lung cancer; immune checkpoint inhibitors; ICI efficacy; survival.

Introduction

Immunotherapy has fundamentally changed the paradigm of treating metastatic non-small cell lung cancer (mNSCLC) (Capella et al., 2024). Unlike the cytotoxic effects of chemotherapy, immune checkpoint inhibitors (ICIs) target immune cells and restore suppressed antitumor immunity. This effect is achieved by blocking inhibitory signals that prevent T-cell activation and cytotoxic immune responses directed at tumor cells (Jin et al., 2023). Despite the large number of ICIs approved in Europe and North America for the treatment of mNSCLC, only monoclonal antibodies blocking programmed cell death receptors (PD-1) and their ligands (PD-L1) are approved in Ukraine. Pembrolizumab and atezolizumab provide a prolonged clinical response and are widely used for treating mNSCLC in Ukraine.

Despite significant improvements in survival, some patients with mNSCLC receiving ICI therapy experience serious adverse effects. Typically, immune checkpoints ensure immune tolerance. Blocking ICI receptors leads to the emergence of autoreactive T cells and autoimmune reactions (Weinmann & Pisetsky 2019). Immune-related adverse events (irAEs) of any severity can occur in 70% of patients receiving PD-1/PD-L1 inhibitors, and approximately 15% of patients have experienced moderate or severe irAEs (Huang et al., 2024).

Corticosteroids (CSs), known for their anti-inflammatory properties, are widely used to manage immunotherapy-related complications. CSs suppress the expression of pro-inflammatory genes and inhibit immune responses by IL-2-mediated T-cell activation and an increase in regulatory T cells (Bruera & Suarez-Almazor, 2022). Additionally, steroids influence the microbiome, macrophage polarization in the tumor microenvironment, lymphocyte infiltration, tumor antigen release, and immune-mediated tumor destruction (Jove et al., 2019). Overall, some effects of CSs are directly opposed to those of ICIs. In oncology, CSs are used not only for the management of irAEs. Due to their anti-edematous, anti-inflammatory, anti-allergic, and analgesic effects, steroid hormones are effective in oncologic emergencies (e.g., superior vena cava syndrome, intracranial hypertension) and in treating cancer-related symptoms (e.g., symptomatic brain metastases, cachexia, spinal cord compression). Moreover, they are successfully used in palliative therapy (for pain, fatigue, dyspnea) and for managing comorbidities (e.g., rheumatoid arthritis, chronic obstructive pulmonary disease (COPD), allergies) (Kalfeist et al., 2022).

The increasing use of ICIs alongside the widespread application of steroids in oncology underscores the importance of understanding their mutual effects. Numerous studies have confirmed the negative impact of systemic corticosteroids (SCSs) on the effectiveness of immunotherapy in patients with mNSCLC (De Giglio et al., 2022; Goodman et al., 2023; Li et al., 2023). However, the effect of inhaled corticosteroids (ICSs) on patient survival remains unclear. This study aimed to evaluate the impact of SCSs and ICSs on the effectiveness of ICI therapy in patients with mNSCLC.

Materials and methods

The study was conducted in accordance with the Declaration of Helsinki and approved by the Commission on Bioethics in Experimental and Clinical Research of the Educational and Scientific Medical Institute of Sumy State University (№ 3/12, date of approval 17 December 2024). Informed consent was obtained from all subjects involved in the study.

This single-center cohort study was conducted at the Sumy Regional Clinical Oncology Center and included 105 patients who received ICI therapy between 2016 and 2024. Inclusion criteria were histologically confirmed mNSCLC, at least one course of immunotherapy (pembrolizumab or atezolizumab), and age ≥18 years. Patients were excluded if they had small cell lung cancer, non-metastatic disease (stages I–III), or were not treated with pembrolizumab or atezolizumab. We involved 41 patients <60 years old and 64 patients ≥60 years old. The investigated cohort included 16 female and 89 male mNSCLC patients.

Demographic and clinicopathological data were obtained from medical records, including sex, age, comorbidities, dates of immunotherapy initiation, and disease progression. Special attention was given to comorbidities such as COPD, hypertension of any grade, cardiovascular diseases, and diabetes of any type. Mortality data were collected from the Sumy Regional Clinical Oncology Center cancer registry.

CS use history was extracted from medical records, and patients were categorized into three groups: 1) patients not receiving steroids, 2) patients receiving SCSs, and 3) patients receiving ICSs. SCSs included dexamethasone, methylprednisolone, and prednisolone. A prednisolone-equivalent dose of ≥10 mg was considered supraphysiologic and classified as SCS use. ICSs included beclomethasone, budesonide, and fluticasone, excluding intranasal forms.

Radiologic response to treatment was assessed according to the Immune Response Evaluation Criteria in Solid Tumors (iRECIST). Objective response rate (ORR) was defined as the percentage of patients achieving complete response (CR) or partial response (PR) to therapy. Disease control rate (DCR) was calculated as the total percentage of patients achieving CR, PR, or stable disease (SD). Progression-free survival (PFS) was calculated as the time from the first ICI infusion to radiologic disease progression. Overall survival (OS) was calculated as the time from the first ICI infusion to death.

Baseline clinicopathological characteristics of categorical variables were presented as the number and percentage of patients. The association between variables and steroid therapy was analyzed using the chi-square test. Survival curves were visualized using the Kaplan-Meier method, and differences in survival across groups were assessed using the log-rank test. Cox proportional hazard regression was employed to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) for PFS and OS. A significance threshold of $P < 0.05$ was applied. Statistical analyses and visualizations were performed using Stata, version 18.0.

Results

The study included 105 patients with mNSCLC, including 38 who received SCSs, 16 who received ICSs, and 51 who did not receive any CSs. SCS and ICS therapy was more common among patients aged ≥60 years ($\chi^2 = 4.456$; P = 0.035). ICS use was associated with COPD ($\chi^2 = 14.118$; P = 0.0001). Clinicopathological characteristics are presented in Table 1.

The median follow-up period before registration of disease progression was 7.0 months. Patients receiving SCSs had significantly worse PFS than those who did not receive steroids or used ICSs. The median PFS was 8.6 months, 4.1 months, and 16.8 months for patients with no steroids, those receiving SCSs, and those receiving ICSs, respectively (Log-rank P = 0.0001, Fig. 1).

The median follow-up period before death due to disease progression or other causes was 14.8 months. Patients using SCSs had significantly worse OS than those not using CSs or ICSs. The median OS was 20.1, 6.9, and 35.1 months for patients with no steroids, those receiving SCSs, and those receiving ICSs, respectively (Log-rank P = 0.0001, Fig. 2).

The ORR for the investigated cohort was 51.4%, while the DCR was 86.6%. Significant differences in ORR and DCR were observed among groups. Patients using ICSs exhibited superior ORR and DCR ($\chi^2 = 23.121$, P = 0.0001 and $\chi^2 = 8.805$, P = 0.012, respectively; Table 2, Fig. 3).

Multivariate regression analysis demonstrated that the use of SCS (HR = 3.94, 95% CI 2.29–6.79, P = 0.0001) and the presence of COPD (HR = 0.15, 95% CI 0.05–0.46, P = 0.001) were independent prognostic factors for PFS. Patients who received SCSs during ICI therapy and those without COPD had worse PFS compared to patients who did not receive SCSs and had COPD.

Table 1
Clinicopathological characteristics of patients stratified by corticosteroid therapy (n = 105)

Variables	No steroids, n = 51	SCS, n = 38	ICS, n = 16	χ^2 (P)
Age, years				
<60	26 (51.0)	11 (28.9)	4 (25.0)	4.456
≥60	25 (49.0)	27 (71.1)	12 (75.0)	(0.035)
Sex, n (%)				
Male	43 (84.3)	32 (84.2)	14 (87.5)	0.029
Female	8 (15.7)	6 (15.8)	2 (12.5)	(0.864)
Hypertension, n (%)				
Present	13 (25.5)	8 (21.1)	1 (6.2)	2.007
Absent	38 (74.5)	30 (78.9)	15 (93.8)	(0.157)
Diabetes, n (%)				
Present	4 (7.8)	7 (18.4)	0 (0.0)	0.433
Absent	47 (92.2)	31 (81.6)	16 (100.0)	(0.511)
COPD, n (%)				
Present	1 (2.0)	2 (5.3)	15 (93.8)	14.118
Absent	50 (98.0)	36 (94.7)	1 (6.2)	(0.0001)
Cardiovascular disease, n (%)				
Present	3 (5.9)	10 (26.3)	0 (0.0)	3.064
Absent	48 (94.1)	28 (73.7)	16 (100.0)	(0.080)

Note: the chi-square test was used for statistical analysis; SCS – systemic corticosteroids; ICS – inhaled corticosteroids; COPD – chronic obstructive pulmonary disease.

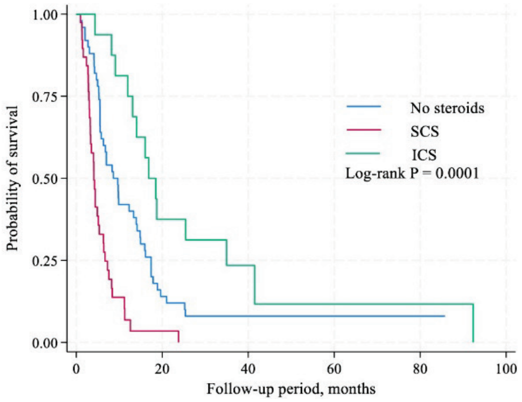

Fig. 1. Comparison of PFS by corticosteroid use in patients with mNSCLC who received ICI therapy (n = 105)

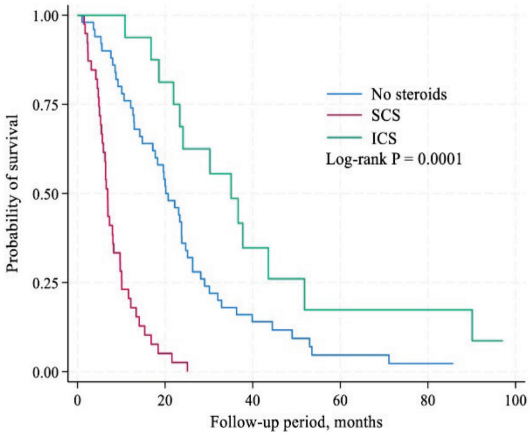

Fig. 2. Comparison of OS by corticosteroid use in patients with mNSCLC who received ICI therapy (n = 105)

Regarding overall OS, independent predictors included SCS treatment (HR = 6.53, 95% CI 3.62–11.76, P = 0.0001), the presence of cardiovascular disease (HR = 2.94, 95% CI 1.43–6.04, P = 0.003), and COPD (HR = 0.17, 95% CI 0.05–0.56, P = 0.004). Unlike COPD, SCS use and the presence of cardiovascular disease negatively impacted OS (Table 3).

Analysis of the impact of SCSs on ICI efficacy. Among 38 mNSCLC patients receiving SCSs, 17/38 (44.7%) were prescribed corticosteroids due to ≥ grade 2 irAEs, while 21/38 (55.2%) received them for cancer-related symptom management (fatigue, pain, cachexia, symptomatic brain metastases). Eighteen patients received long-acting corticosteroids (dexamethasone), while 20 received intermediate-acting corticosteroids (methylprednisolone and prednisolone).

Table 2
Response to ICI therapy stratified by history of steroid use in patients with mNSCLC

Response to treatment	No steroids, n (%)	SCS, n (%)	ICS, n (%)	χ_2 (P)
ORR:				
Yes, 54 patients	31 (60.8)	9 (23.7)	14 (87.5)	23.121
No, 51 patients	20 (39.2)	29 (76.3)	2 (12.5)	(0.0001)
DCR:				
Yes, 91 patients	47 (92.2)	28 (73.7)	16 (100.0)	8.805
No, 14 patients	4 (7.8)	10 (26.3)	0 (0.0)	(0.012)

Note: the chi-square test was used for statistical analysis; ORR – objective response rate; DCR – disease control rate; SCS – systemic corticosteroids; ICS – inhaled corticosteroids.

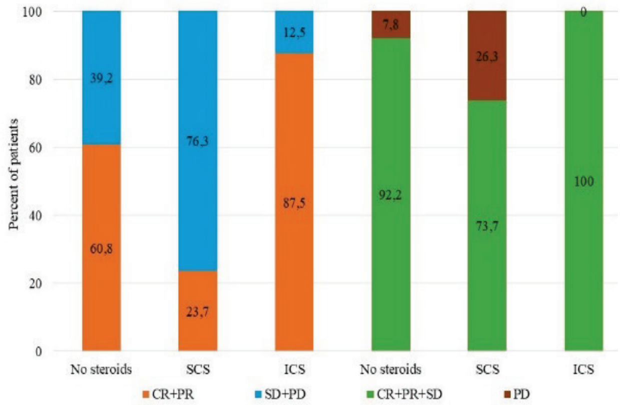

Fig. 3. Response to treatment according to the history of corticosteroid use in patients with mNSCLC who received ICI therapy (n = 105)

Table 3
Identification of independent predictors of PFS and OS in the studied cohort

Variables	PFS			OS		
	HR	95% CI	P	HR	95% CI	P
Age (<60 versus ≥60 years)	1.13	0.72–1.78	0.575	1.46	0.92–2.31	0.105
Sex (male versus female)	1.06	0.60–1.87	0.834	1.10	0.62–1.34	0.738
Hypertension (absent versus present)	2.06	1.21–3.53	0.058	2.26	1.32–3.85	0.053
Diabetes (absent versus present)	0.91	0.43–1.92	0.810	1.16	0.58–2.29	0.669
COPD (absent versus present)	0.15	0.05–0.46	0.001	0.17	0.05–0.56	0.004
Cardiovascular disease (absent versus present)	2.01	0.98–4.10	0.054	2.94	1.43–6.04	0.003
Steroids use (SCS versus no steroids)	3.94	2.29–6.79	0.0001	6.53	3.62–11.76	0.0001
Steroids use (ICS versus no steroids)	2.84	0.91–8.83	0.071	2.48	0.68–9.03	0.167

Note: SCS – systemic corticosteroids; ICS – inhaled corticosteroids; COPD – chronic obstructive pulmonary disease; PFS – progression-free survival; OS – overall survival.

We examined the association between ICI efficacy and the type of corticosteroid used. Patients receiving long-acting SCSs had significantly worse OS than those receiving intermediate-acting SCSs. The median OS was 9.7 months and 4.7 months for patients using intermediate-acting and long-acting SCSs, respectively (Log-rank P = 0.0001). Long-acting SCSs were primarily prescribed for cancer symptom management (85.7%), while intermediate-acting SCSs were used exclusively for irAE management (100.0%).

Thus, it can be assumed that intermediate-acting SCSs did not worsen survival in patients who developed irAEs. In contrast, long-acting SCSs used for symptom control reduced ICI efficacy and worsened OS (Fig. 4).

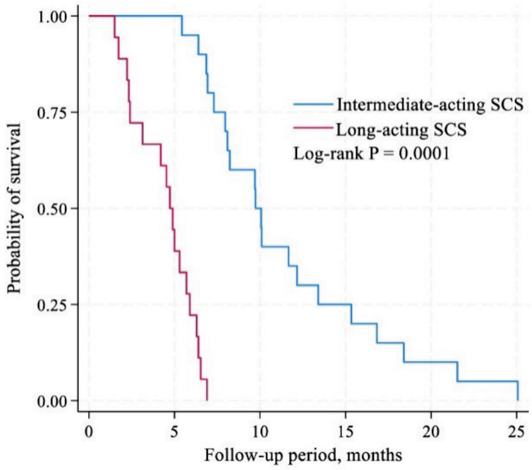

Fig. 4. Differences in OS among mNSCLC patients receiving intermediate- versus long-acting SCSs (n = 105)

Discussion

In this study, we found that SCSs reduced the efficacy of ICIs in patients with mNSCLC. In contrast, ICS use was associated with improved PFS and OS, particularly in patients with COPD. Multivariate analysis confirmed that SCS use was an independent predictor of poor prognosis, whereas COPD was identified as a positive prognostic factor. We assessed the relationship between corticosteroid type and ICI efficacy. It was found that long-acting SCSs (dexamethasone), which were prescribed for cancer symptom management, reduced ICI efficacy. Meanwhile, intermediate-acting SCSs, mainly used for irAE management, did not negatively impact OS.

Immunotherapy is a modern and effective treatment for advanced lung cancer. The immune-modulating effect of ICIs is directly opposed to that of corticosteroids. However, in many cases, corticosteroids in oncology are unavoidable. Patients with mNSCLC often have multiple comorbidities requiring SCS therapy. Additionally, corticosteroids are indispensable for treating irAEs and cancer-related symptoms. Therefore, a clear understanding of the impact of SCSs and ICSs on ICI efficacy is crucial (Cortellini et al., 2020; Hong et al., 2024).

Several studies have demonstrated the negative impact of SCSs on NSCLC treatment outcomes. Ricciuti et al. (2019) found that patients receiving ≥10 mg of prednisolone at the start of immunotherapy had worse PFS and OS compared to those receiving <10 mg. Scott et al. (2018) demonstrated that SCS use reduced clinical benefit and survival in patients treated with nivolumab.

The underlying mechanism of this negative effect is the suppression of T-cell differentiation and proliferation, leading to immunosuppression (Giles et al., 2018; Vynnychenko et al., 2025). Our study confirmed the detrimental impact of SCSs on PFS and OS. However, subgroup analysis revealed that intermediate-acting SCSs did not worsen survival. These steroids were primarily used for irAE management. Our findings align with those reported by Skribek et al. (2021), who studied 196 mNSCLC patients, 46.3% of whom received SCSs during immunotherapy. The authors found that SCSs prescribed for irAE management did not reduce ICI efficacy, whereas steroids used for cancer symptom relief negatively affected prognosis.

ICSs are widely used in pulmonology. Pitre et al. (2022) conducted a meta-analysis showing that ICS use was associated with a reduced risk of lung cancer, particularly in COPD patients. Similar findings were reported by Tareke et al. (2022), who demonstrated that ICS reduces lung cancer risk by 31% in COPD patients. The anti-inflammatory effect of ICSs is attributed to their localized action on immune cells, particularly alveolar macrophages, which are significantly increased in COPD patients. These cells produce pro-inflammatory cytokines and chemokines, notably interleukin-8 (IL-8), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α). ICSs inhibit the release of these mediators and reduce local inflammation. Their effect on CD4+ and CD8+ T cells remains ambiguous. Although a temporary reduction of the number of these cells occurs, this effect is short-term and does not result in systemic immunosuppression (Lea et al., 2023).

A literature search yielded no data on the impact of ICSs on ICI efficacy. However, some reports suggest an increased risk of irAEs in COPD patients receiving ICI therapy (Zhang et al., 2022). Li et al. (2020) reported that patients ≥65 years old who used ICSs at the start of ICI therapy had a slightly higher incidence of autoimmune pneumonitis. However, other authors refute these findings (Zeng et al., 2022).

Since most patients in our cohort used ICSs for COPD treatment, it can be assumed that the improved survival was due to the immune-modulatory effects of COPD rather than the ICSs themselves. Several studies have examined the impact of COPD on the tumor microenvironment. Mark et al. (2028) found that COPD increased CD4+ and CD8+ T-cell numbers and shifted the tumor microenvironment toward a pro-inflammatory condition. Consequently, lung cancer patients with COPD receiving ICIs demonstrated a better response to treatment, leading to longer PFS and OS (Shin et al., 2019; Qi et al., 2022). Some authors propose that COPD should be considered a prognostic factor for ICI efficacy (Zhou et al., 2021). Our multivariate analysis confirmed the positive prognostic value of COPD. The improved survival observed in patients using ICSs for COPD symptom relief suggests that ICSs do not negatively impact ICI efficacy.

This study is limited by its single-center, retrospective design. Additionally, we did not assess the impact of steroid therapy initiation timing or duration on ICI efficacy. We also did not evaluate patients' mutational status or the effects of specific treatment regimens on survival outcomes.

Conclusions

SCSs, particularly long-acting forms, reduce ICI efficacy and are independent predictors of poor prognosis. ICS use does not worsen treatment outcomes. COPD in mNSCLC patients is a prognostic factor for a better response to immunotherapy.

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The authors declare no conflict of interest.

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