BRIEF REPORT

Early Use of Systemic Corticosteroids in Patients with Advanced NSCLC Treated with Nivolumab

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Received 30 May 2018; accepted 13 June 2018
Available online - 20 June 2018

ABSTRACT

Introduction: Checkpoint inhibitors augment the immune system's natural surveillance mechanisms and have increasing applications in NSCLC. Immunosuppressive corticosteroids are also frequently used in this population to treat unwanted inflammation. In view of this mechanistic opposition, we investigated the interaction between nivolumab and corticosteroids in patients with advanced NSCLC.

Methods: A retrospective review of the charts of 210 patients with NSCLC who were treated with nivolumab at the Cleveland Clinic was performed. Use of systemic corticosteroids (equivalent to >10 mg of prednisone/d) during nivolumab therapy was associated with the objective outcomes number of nivolumab cycles and overall survival.

Results: In all, 66 patients (31%) received concurrent systemic corticosteroids during nivolumab therapy. The most common indications included sequelae from active or treated brain metastases (27%) and chronic obstructive pulmonary disease or other respiratory disease (21%). For patients with early exposure to steroids (within the first 30 days of nivolumab therapy) (12% [n=25]), the median number of nivolumab cycles was 2, compared with five cycles in patients who were not exposed to corticosteroids ($p = 0.002$). The median overall survival time for patients who received steroids during the first 30 days was 4.3 months, compared with 11 months for patients who did not receive steroids (hazard ratio for death = 2.30, 95% confidence interval: CI 1.27–4.16, $p = 0.006$ in multivariate analysis).

Conclusion: Nearly one-third of patients with NSCLC treated with nivolumab were prescribed concurrent corticosteroids during the course of nivolumab therapy. Patients exposed to corticosteroids during the first cycle of nivolumab received fewer total cycles of nivolumab, suggesting decreased clinical benefit, and they had shorter overall survival.

Keywords: NSCLC; immuno-oncology; nivolumab; corticosteroids

Introduction

Lung cancer is the leading cause of cancer-related deaths.[1] In recent years novel immune checkpoint inhibitors (ICIs), including the programmed death 1 (PD-1) inhibitor nivolumab, have been incorporated as second-line treatment for NSCLC and also as first-line therapy in select patients.[2–5]

Tumors evade natural immunosurveillance mechanisms by manipulating checkpoint signals intended to prevent autoimmunity. Programmed death ligand 1 expressed on tumor cells binds PD-1 receptors on T lymphocytes, leading to downregulation of their cytotoxic antitumor effect. ICIs were developed to prevent this immune evasion and enhance the immune system's inherent antitumor activity.[6]

In contrast, corticosteroids are used for treatment and prevention of unwanted inflammation, which theoretically undermines the therapeutic mechanism of ICIs. Corticosteroids have multiple mechanisms of action that lead to decreased inflammation and immune activity, including lymphopenia and impaired T-cell response to antigen.[7] Many patients with NSCLC require corticosteroids before, during, or after treatment with ICIs (for example, those with symptomatic brain metastases or exacerbations of chronic obstructive pulmonary disease).

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Disclosure: Dr. Pennell reports personal fees from AstraZeneca, Eli Lilly, and Regeneron outside the submitted work. The remaining author declares no conflict of interest.

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ISSN: 1556-0864
https://doi.org/10.1016/j.jtho.2018.06.004

In addition, inhibition of immune regulatory checkpoints that induce tolerance underlies most of the adverse effects of ICIs, predominantly in the form of autoimmune toxicities. These immune-related adverse events (irAEs) are universally treated with corticosteroids.[8]

On the basis of this mechanistic opposition, it is presumed that immunosuppression by corticosteroids may hinder the efficacy of ICIs. Patients receiving systemic steroids at baseline have been excluded from clinical trials,[2,3,9] so the true significance of this interaction remains unknown. Reports on patients with melanoma treated with the cytotoxic T-lymphocyte associated protein 4 inhibitor ipilimumab have observed that antitumor effects persist in patients with irAEs who were treated with high-dose steroids.[10,11] In contrast, whether steroids affect the initial antitumor response of immunotherapies is unknown.

The goal of this study was to assess outcomes of patients with advanced NSCLC who were treated with nivolumab and also received systemic corticosteroids, particularly during the initiation of immunotherapy.

Materials and Methods

Approval for this research was obtained by the institutional review board of the Cleveland Clinic. Patients were identified by pharmacy record review of nivolumab therapy initiated at the Cleveland Clinic from April 2015 to April 2016, including 18 clinical sites and 34 individual providers. Patient data were collected until death or last clinical visit through April 2017. The study population included only patients with histologically confirmed NSCLC. Those who received at least one complete cycle (two doses) of nivolumab at a dose of 3 mg/kg on days 1 and 14 of a 28-day cycle were included in analysis.

Use of systemic steroids was recorded for oral or intravenous doses with an equivalent dose higher than 10 mg of prednisone daily on the basis of the exclusion criteria for randomized controlled trials in this population.[2,3,9]

Continuous variables were compared by using the Mann-Whitney test and categorical variables were compared by using the χ^2 test. The Kaplan-Meier method was used to estimate overall survival from the start of nivolumab therapy to death, and the log-rank test was used to compare survival between groups. A multivariable Cox proportional hazards model estimated the risk associated with steroid use in the setting of additional predictors, including sex, race, smoking history, histologic subtype, time since diagnosis, Eastern Cooperative Oncology Group performance status, and prior brain metastases. Statistical analysis was performed using STATA software (version 14.0, Stata Corp LP, College Station, TX).

Results

Pharmacy records identified 244 patients with histologically confirmed NSCLC who started receiving nivolumab between April 2015 and April 2016. Six patients did not receive their full course of treatment at our institution or were lost to follow-up before completion of therapy and were therefore excluded from further analysis. Two patients who had previously received the ICI pembrolizumab were also excluded. Of the remaining 236 patients, 26 received only one dose of nivolumab and did not complete a full cycle; thus, they were not included in further analysis.

The patients' characteristics are presented in Table 1. The median time from diagnosis of NSCLC to initiation of nivolumab was 13.4 months. Nearly two-thirds of the patients (n = 137) died during the 2 years of review, and the median overall survival was 10.7 months for all patients treated with nivolumab. In all, 30 patients (14%) continued nivolumab therapy past the end of data collection.

A total of 66 patients (31%) received systemic steroids at an equivalent daily dose higher than 10 mg of prednisone while taking nivolumab. There was no difference in steroid use by demographic group, histologic subtype, duration of lung cancer, or Eastern Cooperative Oncology Group performance status (see Table 1). Patients with brain metastases before the initiation of nivolumab therapy were more likely to receive steroids while being treated with nivolumab ($p = 0.04$). The most common indications for concurrent administration of corticosteroids included sequelae from active or treated brain metastases such as radiation necrosis (27% [n = 18]), chronic obstructive pulmonary disease or other respiratory disease (21% [n = 14]), and disease-related pain and constitutional symptoms such as fatigue and anorexia (18% [n = 12]) (Table 2). Daily doses of corticosteroids ranged from at least than 10 mg daily to 180 mg daily, with a median initial dose of 35 mg of prednisone (or equivalent) per day. Duration of corticosteroid use was not amenable to rigorous analysis owing to the individualized dose tapers and recurrent courses.

For patients receiving immunosuppressive doses of steroids at initiation or within the first 30 days of nivolumab therapy (12% [n = 25]), the median number of nivolumab cycles was two (range 1–16 cycles), compared with five cycles (range 1–21) in patients who were not exposed to corticosteroids during that time ($p = 0.002$). Similarly, the median overall survival for patients receiving steroids during their first cycle was 4.3 months (95% confidence interval [CI]: 2.6–9.7), compared with 11 months for patients not taking steroids (95% CI: 9.6–13.8). Kaplan-Meier survival estimates are shown in Figure 1, with a log-rank p value of 0.017. Survival was also significantly shorter when only

Table 1. Use of Concurrent Corticosteroids at Any Time during Nivolumab Therapy in Patients with Advanced NSCLC

Characteristic	No Steroids	Concurrent Steroids	Total	*p* Value
Sex				
Male	78 (54%)	35 (53%)	113 (54%)	0.89
Female	66 (46%)	31 (47%)	97 (46%)	
Age at start of nivolumab therapy, y				
Median (IQR)	68.5 (62-74)	66 (58-73)	67.5 (60-74)	0.084
Race				
White	117 (81%)	55 (83%)	172 (82%)	0.716
Other	27 (19%)	11 (17%)	38 (18%)	
Smoking history				
Current or former smoker	124 (86%)	62 (94%)	186 (89%)	0.098
Never-smoker	20 (14%)	4 (6%)	24 (11%)	
Histologic subtype				
Nonsquamous carcinoma	110 (76%)	48 (73%)	158 (75%)	0.57
Squamous cell carcinoma	34 (24%)	18 (27%)	52 (25%)	
Time since diagnosis[a]				
Median (IQR)	13.5 (7-24)	14.1 (8-29)	13.4 (7-25)	0.72
ECOG performance status				
0	29 (20%)	10 (15%)	39 (19%)	0.34
1	56 (39%)	35 (53%)	91 (43%)	
2	8 (6%)	5 (8%)	13 (6%)	
Unknown	51 (35%)	16 (24%)	67 (32%)	
Prior brain metastasis[b]				
No	113 (78%)	43 (65%)	156 (74%)	0.04
Yes	31 (22%)	23 (35%)	54 (26%)	

[a]Months from NSCLC diagnosis to start of nivolumab therapy.
[b]Brain metastasis diagnosed before start of nivolumab therapy.
IQR, interquartile range; ECOG, Eastern Cooperative Oncology Group.

the subgroup of patients receiving steroids on the first day of nivolumab treatment (n = 12) were compared with those not receiving steroids at the initiation of nivolumab therapy ($p = 0.02$). In multivariate analysis, the use of steroids in the first 30 days remained significantly associated with increased risk of death (hazard ratio = 2.30, 95% CI: 1.27–4.16, $p = 0.006$) (Table 3).

irAEs requiring steroid therapy were recorded in 31 patients who received nivolumab (15%). As already noted, either steroids were prescribed concurrently with nivolumab or nivolumab was resumed after steroid treatment in 11 patients (see Table 2). The remaining 20 patients did not receive steroids concurrently, as nivolumab was discontinued at onset of the adverse event and patients were subsequently treated with corticosteroids. Among all 31 patients with immune-related nivolumab toxicity requiring steroid treatment, the overall survival was not significantly different from that among patients without these events, with median overall survival times of 16.1 months (95% CI: 7.6–18.5) and 10.5 months (95% CI: 8.6–12.2), respectively ($p = 0.50$).

Table 2. Indications for Concurrent Corticosteroid Use in Patients with NSCLC Who Are Undergoing Nivolumab Therapy

Indication for Concurrent Steroid Therapy	No. of cases (%)
Brain metastases/radiation necrosis	18 (27%)
COPD or respiratory symptoms[a]	14 (21%)
Constitutional symptoms	12 (18%)
Immune-related adverse effects	11 (17%)
Other/multiple indications	11 (17%)

[a]Pneumonitis or clinical suspicion of pneumonitis was not included in this group of symptoms, but was included in immune-related adverse effects.
COPD, chronic obstructive pulmonary disease.

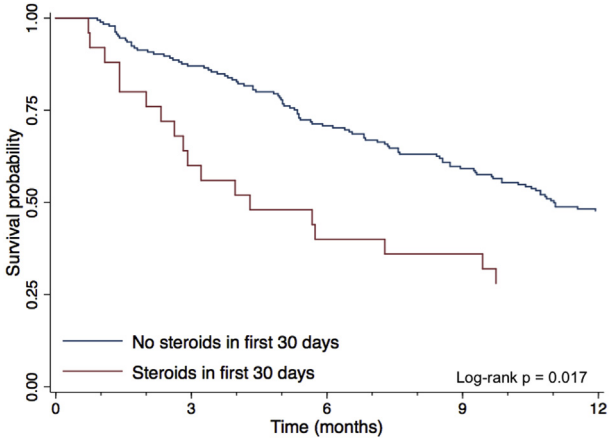

Figure 1. Kaplan-Meier estimate of overall survival from the start of nivolumab therapy according to exposure to systemic corticosteroids during the first 30 days of nivolumab therapy.

Table 3. Multivariate Cox Proportional Hazards Model for Patients Taking Nivolumab, Including Concurrently with Corticosteroids

Characteristic	Hazard Ratio	95% CI	*p* Value
Sex (ref = male)			
Female	1.03	0.66-1.62	0.88
Age (per year)	1.02	1.00-1.05	**0.04**
Race (ref = white)			
Other race	0.64	0.36-1.14	0.13
Smoking history (ref = never-smoker)			
Current or former smoker	0.77	0.41-1.43	0.40
Histologic subtype (ref = nonsquamous)			
Squamous	1.35	0.80-2.26	0.26
Time since diagnosis[a] (per month)	0.99	0.98-1.00	0.16
ECOG performance status (ref = 0)			
1	1.13	0.68-1.86	0.64
2	1.39	0.72-3.48	0.24
Prior brain metastasis[b] (ref = no)			
Yes	1.19	0.74-1.90	0.47
Steroids in first 30 days (ref = none)			
Steroids given	2.30	1.27-4.16	**0.006**

Boldface indicates statistical significance.
[a]Months from diagnosis NSCLC to start of nivolumab therapy.
[b]Brain metastasis diagnosed before the start of nivolumab therapy.
CI, confidence interval; ECOG, Eastern Cooperative Oncology Group.

Discussion

Systemic corticosteroids theoretically undermine the immunomodulatory effect of ICIs such as nivolumab. In this study population, nearly one-third of patients with advanced NSCLC who were being treated with nivolumab required corticosteroids during the course of their treatment. Patients receiving immunosuppressive doses of corticosteroids exceeding 10 mg of prednisone daily (or the equivalent) were excluded from clinical trials of nivolumab, and what effect these drugs have on the efficacy of or response to ICIs is unknown.

In this single-center population, nearly one-third of patients received concurrent corticosteroids while taking nivolumab, including 12% of patients who received corticosteroids during the first 30 days of nivolumab therapy. Patients treated with steroids early in their course received fewer total nivolumab treatments than did patients who did not receive steroids early on, suggesting a decreased rate of response to therapy in the steroid group. These patients also had significantly shorter overall survival. In contrast, there was no apparent difference in survival among patients treated with steroids for irAEs. However, this group represents a heterogeneous group of patients who progressed early during nivolumab therapy or discontinued steroids early on account of toxicity, as well as long-term responders in whom toxicity developed late in their course.

In addition, it may be that not all early steroid use is detrimental, as illustrated by improved PFS and OS with the addition of the anti–programmed death ligand 1 agent atezolizumab to chemotherapy in a recently presented phase 3 trial in first-line NSCLC,[12] with steroids used as standard premedication. However, the duration of steroid treatment was very short and limited to the peri-chemotherapy period, which may not have affected efficacy. Examining the relationship between timing and duration of steroid administration in future studies will be very important.

Limitations of this study include the inability to isolate steroid use as an independent variable in a diverse group of patients with advanced disease, significant comorbidities associated with the likelihood of steroids use, and a low expected rate of response to nivolumab. Ideally, we would incorporate objective characterization of treatment response by using radiographic data according to the Response Evaluation Criteria in Solid Tumors or newer immune-related response criteria,[13] but this was not possible owing to the varied intervals of imaging between individual patients, as well as to the lack of available imaging review for all patients. Whether the need for steroids is an independent indicator of progression or lack of response to therapy (which we cannot determine from this retrospective study) should also be considered.

This study showed that, unlike in the population of patients in phase 3 trials, immunosuppressive corticosteroid use is prevalent among patients with NSCLC who are receiving nivolumab, emphasizing the importance of understanding the nature of their interaction. As we gain more experience with nivolumab and other ICIs, a better understanding of these diverse immunomodulatory effects will ideally improve therapeutic responses and patient outcomes. With the expanding application of ICIs in all stages of NSCLC, prospective studies of patients treated with and without concurrent corticosteroids will, it is hoped, elucidate the role of corticosteroids in immuno-oncology and help guide clinicians in management of these therapies.

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