BRIEF REPORT

Clinical Outcomes of Patients With Metastatic NSCLC After Discontinuation of Immunotherapy Because of Immune-Related Adverse Effects

Lysanne A. Lievense, MD, PhD,* Peter Heukels, MD, PhD, Nico C. van Walree, MD, Cor H. van der Leest, MD, PhD

Department of Pulmonary Medicine, Amphia Hospital, Breda, The Netherlands

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ABSTRACT

Introduction: Immune checkpoint inhibition (ICI) is an important treatment modality in metastatic NSCLC and management of immunotherapy-related adverse effects (irAEs) can be challenging. Retreatment after discontinuation of ICI because of irAEs is a frequent clinical dilemma with limited available data.

Methods: This single-center retrospective observational study reviewed the clinical course of 30 patients with metastatic NSCLC in whom ICI had to be discontinued owing to a serious irAE after an initial objective response to therapy.

Results: After ICI discontinuation, 14 patients (47%) developed a durable response of more than 6 months, seven patients (23%) developed oligoprogression treated with local radiotherapy leading to disease control, six patients (20%) had progression of disease within 6 months, and three patients (10%) died owing to a severe irAE.

Conclusions: A watchful waiting approach is justified after discontinuation of ICI owing to irAEs in patients with metastatic NSCLC with an initial response to therapy.

Keywords: Non–small cell lung cancer; Immunotherapy; Immune-related adverse effects; Clinical outcomes

Introduction

Immune checkpoint inhibition (ICI) has revolutionized the treatment landscape of fit patients with advanced NSCLC and substantially improved the clinical outcome in patient subsets.[1,2] Compared with conventional cytotoxic or targeted anticancer drugs, ICI dictates a different approach regarding response evaluation and management of treatment-related toxicities.[3] Immune-related adverse effects (irAEs) occur in 30% to 40% of ICI-treated patients.[3] In patients with advanced NSCLC, currently only programmed cell death protein-1 and programmed death-ligand 1–blocking antibodies are approved, and in 3% to 12% of patients, this treatment is discontinued owing to irAEs.[4] When serious irAE occurs, immunotherapy is discontinued and systemic immunosuppressive therapy is often started. Evidently, the occurrence of a life-threatening irAE is an absolute contraindication to restarting ICI. However, a frequent clinical dilemma is whether to resume immunotherapy after the resolution of serious irAEs.[5] Data from clinical trials regarding this issue are limited because immunotherapy is often permanently withdrawn after a serious irAE in clinical studies.

Only limited observational and retrospective data are available regarding the safety and efficacy of ICI

*Corresponding author.

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Address for correspondence: Lysanne A. Lievense, MD, PhD, Department of Pulmonary Medicine, Amphia Hospital, Molengracht 21, 4818 CK Breda, The Netherlands. E-mail: slievense@amphia.nl

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Table 1. Patient Characteristics

Characteristics	n (%)
All, n (%)	30 (100)
Histological subtype, n (%)	
Nonsquamous cell carcinoma	20 (67)
Squamous cell carcinoma	7 (23)
NOS	3 (10)
PD-L1 expression, n (%)	
≥50%	16 (53)
1%-49%	2 (7)
<1%	5 (17)
Unknown	7 (23)
Treatment regimen n (%)	
Pembrolizumab monotherapy	17 (57)
Nivolumab monotherapy	9 (30)
Pembrolizumab + chemotherapy	4 (13)
irAE	n(%)
Pneumonitis	9 (30)
Colitis	9 (30)
Hepatitis	9 (30)
Nephritis	2 (7)
Arthritis	1 (3)
Steroid treatment, n (%)	27 (90)

irAE, immune-related adverse event; NOS, not otherwise specified; PD-L1, programmed death-ligand 1.

rechallenge after a resolved irAE in patients with NSCLC and there is currently no consensus regarding the follow-up treatment regimen.

This study aimed to evaluate the management and clinical outcomes of patients with metastatic NSCLC in our facility who discontinued ICI owing to irAEs after an initial treatment response.

Materials and Methods

In this single-center retrospective observational study, we reviewed all patients with metastatic NSCLC treated in our department with ICI between January 2015 and July 2021. Amphia hospital is a Dutch regional teaching hospital where approximately 400 newly diagnosed patients with lung cancer are treated per year. All patients with metastatic NSCLC in whom ICI had to be withdrawn on the basis of serious irAEs were selected. Nivolumab (3 mg/m^2) was administered every 2 weeks and pembrolizumab (200 mg fixed dosage) was administered every 3 weeks. The evaluation of toxicity was based on the Common Toxicity Criteria for Adverse Events, version 4.0. Before discontinuation of therapy, there had to be a reported objective response to ICI (complete response or partial response). Treatment responses of the patients were evaluated according to the Response Evaluation Criteria in Solid Tumors using whole-body computed tomography performed every 8 to 12 weeks. After a review of the patient records, 30 patients met the inclusion criteria. The duration of follow-up was at least 6 months for all patients.

Results

Patients Characteristics

A total of 30 patients met the inclusion criteria. Most of the tumors were nonsquamous cell carcinomas and had a high (≥50%) programmed death-ligand 1 expression. Most patients (n = 17, 57%) were treated with pembrolizumab monotherapy; however, patients treated with nivolumab monotherapy or pembrolizumab with platinum-based chemotherapy were also included. Pneumonitis (30%), hepatitis (30%), and colitis (30%) were the most commonly occurring irAEs (Table 1).

Clinical Outcomes After ICI Discontinuation

A total of 14 patients (47%) developed a durable response of more than 6 months after ICI discontinuation with a median of 18 months (7–24) at the moment of data acquisition. Seven patients (23%) developed oligoprogression treated with local radiotherapy leading to disease control, the median initial response duration was 8 months (3–11) in this group. Six patients (20%) had a progression of disease within 6 months after discontinuation of ICI, requiring a switch to chemotherapy or best supportive care. Unfortunately, three patients (10%) died owing to severe pneumonitis. All three patients died owing to nivolumab-induced pneumonitis, were former smokers, and had a WHO performance status of one when they started immunotherapy. One patient had no severe comorbidities and died owing to refractory pneumonitis despite treatment with high-dose steroids. The two other patients both had an underlying moderate-severe chronic obstructive pulmonary disease and peripheral vascular disease in addition to their metastatic lung cancer. These comorbidities likely attributed to their death owing to pneumonitis (Fig. 1 and Table 2).

Discussion

The current study provides data that support a wait-and-see strategy in patients with metastatic NSCLC with an initial objective response to ICI and who developed irAEs leading to ICI discontinuation.

We found in this real-world retrospective observational study that 47% of patients with metastatic NSCLC, in whom ICI was discontinued owing to irAEs, reached a durable response with a median duration of 18 months, during which no further interventions were necessary. Furthermore, in 23% of patients, oligoprogression occurred after ICI discontinuation, which could be locally treated with radiotherapy resulting in disease control. Therefore, in 70% of our patients who initially

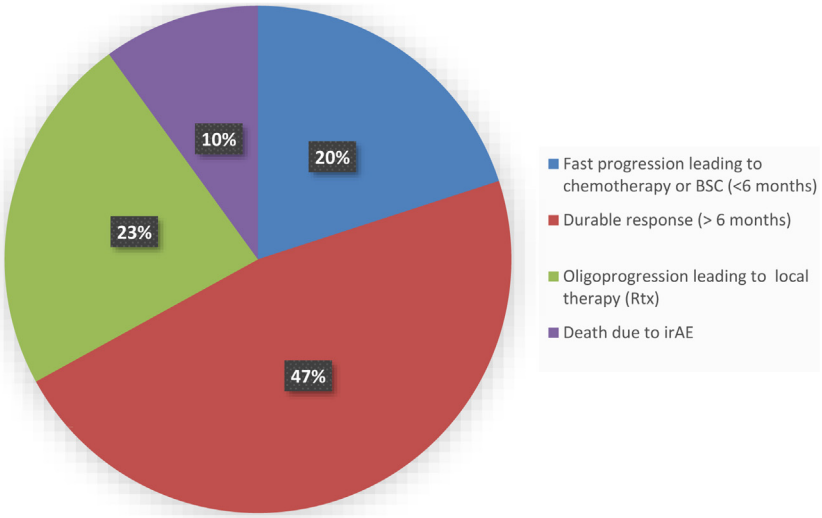

Figure 1. Patient outcomes after ICI discontinuation. ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; BSC, best supportive care; Rtx radiotherapy.

responded to ICI, there was no indication for systemic therapy during 6 months up to 24 months after treatment withdrawal.

Similar results have been found by others in small retrospective studies. Santini et al.[6] described retreatment with ICI did not improve the outcome among 20 patients with metastatic NSCLC who had an initial response but discontinued therapy owing to irAEs. Furthermore, in a study investigating the prognostic relevance of early irAEs, Russano et al.[7] compared 24 patients with metastatic NSCLC in whom ICI had to be discontinued after one administration owing to severe irAEs to controls and found no survival difference.

There are two issues concerning the dilemma of ICI reintroduction after the occurrence of irAEs and initial treatment response—whether it is safe and whether it is necessary.[8,9] Regarding the safety of ICI reintroduction, multiple studies have been published. A recent meta-analysis revealed a higher incidence of all-grade irAEs after rechallenge, but a similar incidence of high-grade irAEs in patients with cancer.[10] In patients with metastatic NSCLC specifically, Santini et al.[6] described in a retrospective study that reintroduction of ICI after irAEs prompting treatment discontinuation and treatment with glucocorticoids did not lead to a recurrence of irAEs in 48% of patients, 26% had a recurrence of the initial irAE, and 26% of patients presented with a new irAE.

The optimal treatment duration in ICI responders is the subject of ongoing extensive research and various clinical trials.[11,12] Current standard of care is to continue ICI for up to 2 years when there is no disease progression or toxicity. In the phase 3b/4 CheckMate 153 study, an exploratory analysis suggested an improved outcome for patients with NSCLC treated continuously with nivolumab versus a fixed duration of 1 year.[13] However, patients with radiographic progression were also included in this study. Clinical trials investigating whether the duration of ICI can be safely shortened in patients with advanced melanoma are currently being performed.

The current study has several limitations. The study design is observational and retrospective, and a relatively small number of patients could be included. Furthermore, the data are heterogenous concerning the follow-up duration and number of ICI courses, which is inherent to the study design. However, there are only very limited data available regarding this subject, which concerns a frequent clinical dilemma. Therefore, this

Table 2. Patient Outcomes After ICI Discontinuation

Patient Outcome	Pt, n (%)	Number of ICI Courses, Median (Range)	OR Duration After ICI Discontinuation, Median (Range), mo
Durable response (>6 mo)	14 (47)	7.5 (3-19)	18 (7-24)
Oligoprogression	7 (23)	11 (3-20)	8 (3-11)
Fast progression (≤6 mo)	6 (20)	4 (2-15)	4.5 (3-6)
Death owing to irAE	3 (10)	9 (3-22)	NA

ICI, immunotherapy; irAE, immunotherapy-related adverse effects; NA, not applicable; OR, objective response; Pt, patient.

study provides real-world data that generate additional insight, which can be used in everyday informed decision-making for clinicians and their patients.

In summary, on the basis of the data presented in this study, we encourage a watchful waiting approach in patients with metastatic NSCLC in whom ICI had to be discontinued owing to irAEs and who achieved an objective response.

CRediT Authorship Contribution Statement

Lysanne A. Lievense: Conceptualization, Data curation, Writing: original draft.

Peter Heukels: Data curation, Writing: review and editing.

Nico C. van Walree: Data curation, Writing: review and editing.

Cor H. van der Leest: Conceptualization, Supervision, Writing: review and editing.

References

1. Gandhi L, Garassino MC. Pembrolizumab plus chemotherapy in lung cancer. *N Engl J Med*. 2018;379:e18.
2. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive non-small-Cell Lung Cancer. *N Engl J Med*. 2016;375:1823–1833.
3. Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. *N Engl J Med*. 2018;378:158–168.
4. Khoja L, Day D, Wei-Wu Chen T, Siu LL, Hansen AR. Tumour- and class-specific patterns of immune-related adverse events of immune checkpoint inhibitors: a systematic review. *Ann Oncol*. 2017;28:2377–2385.
5. Haanen J, Ernstoff M, Wang Y, et al. Rechallenge patients with immune checkpoint inhibitors following severe immune-related adverse events: review of the literature and suggested prophylactic strategy. *J Immunother Cancer*. 2020;8:e000604.
6. Santini FC, Rizvi H, Plodkowski AJ, et al. Safety and efficacy of Re-treating with immunotherapy after immune-related adverse events in patients with NSCLC. *Cancer Immunol Res*. 2018;6:1093–1099.
7. Russano M, Cortellini A, Giusti R, et al. Clinical outcomes of NSCLC patients experiencing early immune-related adverse events to PD-1/PD-L1 checkpoint inhibitors leading to treatment discontinuation. *Cancer Immunol Immunother*. 2022;71:865–874.
8. Akamatsu H, Murakami E, Oyanagi J, et al. Immune-related adverse events by immune checkpoint inhibitors significantly predict durable efficacy even in responders with advanced non-small cell lung cancer. *Oncologist*. 2020;25:e679–e683.
9. Niki M, Nakaya A, Kurata T, et al. Immune checkpoint inhibitor re-challenge in patients with advanced non-small cell lung cancer. *Oncotarget*. 2018;9:32298–32304.
10. Zhao Q, Zhang J, Xu L, et al. Safety and efficacy of the rechallenge of immune checkpoint inhibitors after immune-related adverse events in patients with cancer: a systemic review and meta-analysis. *Front Immunol*. 2021;12:730320.
11. Marron TU, Ryan AE, Reddy SM, et al. Considerations for treatment duration in responders to immune checkpoint inhibitors. *J Immunother Cancer*. 2021;9:e001901.
12. Friedlaender A, Kim C, Addeo A. Rethinking the optimal duration of immune checkpoint inhibitors in non-small cell lung cancer throughout the COVID-19 pandemic. *Front Oncol*. 2020;10:862.
13. Waterhouse DM, Garon EB, Chandler J, et al. Continuous versus 1-year fixed-duration nivolumab in previously treated advanced non-small-cell lung cancer: CheckMate 153. *J Clin Oncol*. 2020;38:3863–3873.