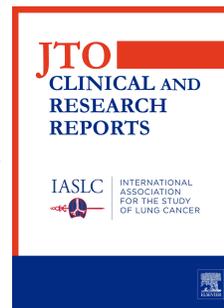


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Brief Report: Clinical outcomes of metastatic non-small cell lung cancer patients after discontinuation of immunotherapy due to immune-related adverse effects

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Abstract

Introduction

Immune checkpoint inhibition (ICI) is an important treatment modality in metastatic non-small cell lung cancer (NSCLC) and management of immunotherapy related adverse effects (irAEs) can be challenging. Retreatment after discontinuation of ICI due to irAEs is a frequent clinical dilemma with limited available data.

Methods

This single-center retrospective observational study reviewed the clinical course of 30 metastatic NSCLC patients in whom ICI had to be discontinued due 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 six months, 7 patients (23%) developed oligoprogression treated with local radiotherapy leading to disease control, 6 patients (20%) had progression of disease within 6 months and 3 (10%) patients died due to a severe irAE.

Conclusions

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

Introduction

Immune checkpoint inhibition (ICI) has revolutionized the treatment landscape of fit advanced non-small cell lung cancer (NSCLC) patients 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 30-40% of ICI-treated patients.³ In advanced NSCLC patients, currently only PD-1/PD-L1 blocking antibodies are approved and in 3-12% of patients this treatment is discontinued due to irAEs.⁴ When serious irAE occur, 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 or not to resume immunotherapy after 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 rechallenge after a resolved irAE in NSCLC patients and there is currently no consensus regarding the follow-up treatment regimen.

The aim of this study was to evaluate the management and clinical outcomes of metastatic NSCLC patients in our facility who discontinued ICI due to irAEs after an initial treatment response.

Methods

In this single-center retrospective observational study we reviewed all metastatic NSCLC patients 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 lung cancer patients are treated per year. All metastatic NSCLC patients in whom ICI had to be withdrawn based on serious irAEs were selected. Nivolumab (3 mg/m²) was administered every 2 weeks and pembrolizumab (200mg fixed dosage) was administered every 3 weeks. The evaluation of toxicity was based on the Common Toxicity Criteria for Adverse Events, version 4.0. Prior to 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 review of the patient records there were 30 patients who met the inclusion criteria. Duration of follow-up was at least six months for all patients.

Results

Patients characteristics

Thirty patients met the inclusion criteria. The majority of the tumors were non-squamous cell carcinomas and had a high ($\geq 50\%$) PD-L1 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 common occurring irAEs.

Table 1 Patient characteristics

All, n(%)	30 (100)
Histology, n (%)	
Non-squamous 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)

Clinical outcomes after ICI discontinuation

Fourteen patients (47%) developed a durable response of more than six months following 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 progression of disease within 6 months after discontinuation of ICI requiring switch to chemotherapy or best supportive care. Unfortunately, three patients (10%) died due to severe pneumonitis. All three patients died due to a nivolumab-induced pneumonitis, were former smokers and had a WHO performance status of 1 when they started immunotherapy. One patient had no severe comorbidities and died due to refractory pneumonitis despite treatment with high dose steroids. The two other

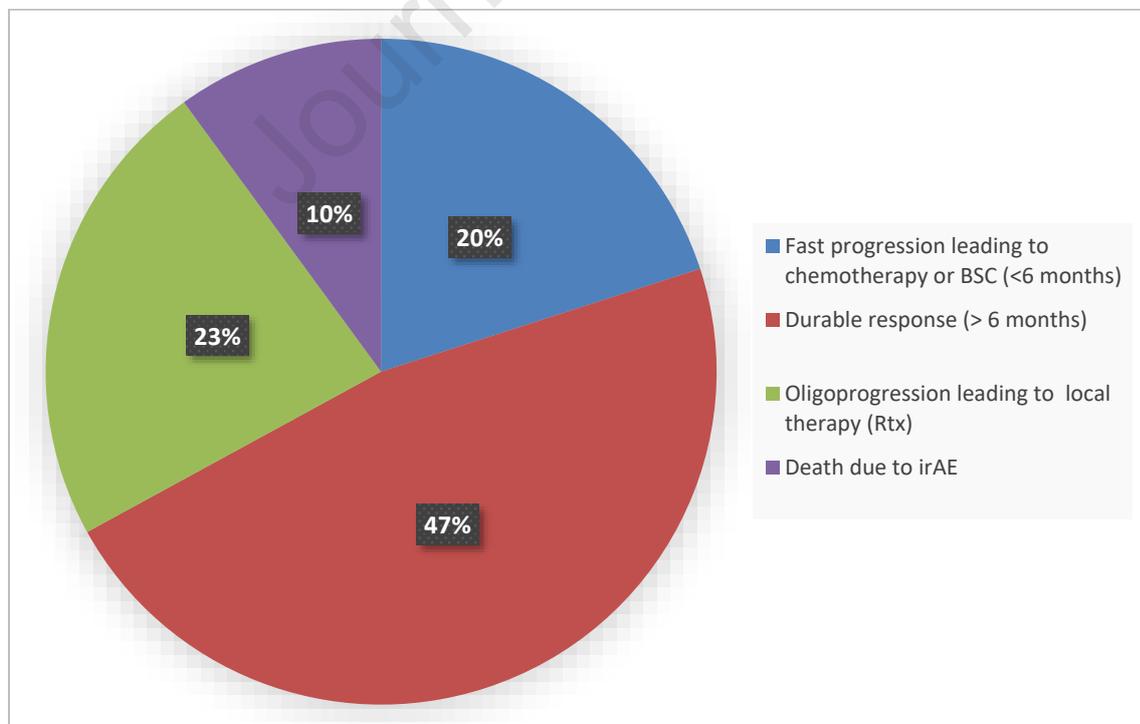
patients both had underlying moderate-severe COPD and peripheral vascular disease in addition to their metastatic lung cancer. These comorbidities likely attributed to their death due to pneumonitis.

Table 2. Patient outcomes after ICI discontinuation

	Pt number (%)	Number of ICI courses, median (range)	OR duration after ICI discontinuation, median (range)
Durable response (>6 months)	14 (47%)	7,5 (3 to 19)	18 months (7-24)
Oligoprogression	7 (23%)	11 (3 to 20)	8 months (3 to 11)
Fast progression (≤ 6 months)	6 (20%)	4 (2 to 15)	4,5 months (3-6)
Death due to irAE	3 (10%)	9 (3 to 22)	NA

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

Figure 1. Patient outcomes after ICI discontinuation



irAE, immune-related adverse events; BSC, best supportive care; Rtx radiotherapy

Discussion

The current study provides data which support a wait-and-see strategy in metastatic NSCLC patients 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 metastatic NSCLC patients, in whom ICI was discontinued due 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 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 described that retreatment with ICI in 20 metastatic NSCLC patients who had an initial response but therapy was discontinued because of irAEs, did not improve outcome.⁶ Furthermore, in a study investigating the prognostic relevance of early irAEs, Russano et al compared 24 metastatic NSCLC patients in whom ICI had to be discontinued after one administration due to severe irAEs to controls and found no survival difference.⁷

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

The optimal treatment duration in ICI responders is subject of ongoing extensive research and various clinical trials.^{11, 12} Current standard of care is to continue ICI for up to two years if there is no disease progression or toxicity. In the phase IIIb/IV Checkmate 153 study, an exploratory analysis suggested an improved outcome for NSCLC patients treated continuously with nivolumab versus a fixed-duration of one year.¹³ However, patients with radiographic progression were also included in this study. Clinical trials to investigate if the duration of ICI can be safely shortened in advanced melanoma patients 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 study does provide real-world data which generate additional insight that can be used in everyday informed decision making for clinicians and their patients.

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

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Credit Statement

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

P. Heukels: Data curation, Writing: reviewing and editing

N.C. van Walree: Data curation, Writing: reviewing and editing

K.H. van der Leest: Conceptualization, Supervision, Writing: reviewing and editing

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