Association Between Immune-related Adverse Events and Efficacy of Immune Checkpoint Inhibitors in Non–small-cell Lung Cancer

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Abstract

Immune checkpoints inhibitors (ICIs) in advanced non–small-cell lung cancer are associated with immune-related adverse events (IRAEs). We retrospectively analyzed the efficacy of ICIs in a cohort of 270 patients with the objective to assess the association of IRAEs with ICI efficacy. We found a statistically significant efficacy difference in favor of patients with IRAEs. These results could be used to determine ICI responders.

Background: Immune checkpoint inhibitors (ICIs) are available for first- and further lines of treatment of patients with advanced non–small-cell lung cancer (NSCLC). These treatments are associated with adverse events called immune-related adverse events (IRAEs). The incidence, diagnosis, and treatment of IRAEs are quite acknowledged; however, the link between IRAEs and the efficacy of ICIs requires further clarification. The objectives of this study were to assess the association between IRAEs incidence and severity and ICIs efficacy in patients with advanced NSCLC. **Methods:** In this retrospective study, clinical, biological, treatment, and outcome data were collected from patients with advanced NSCLC who received at least 1 cycle of ICIs from April 2013 to February 2017. The primary endpoint was to assess the association of IRAEs incidence with overall survival (OS). Secondary endpoints were the association of IRAEs with progression-free survival (PFS), objective response rate (ORR), and disease control rate (DCR). **Results:** Overall, 270 patients were studied. The median OS was 14 months, median PFS was 2.6 months, ORR was 13%, and DCR was 51%. OS, PFS, and ORR were significantly better for patients with IRAEs compared with patients with no IRAEs, translating to median OS not reached versus 8.21 months, respectively (hazard ratio, 0.29; 95% confidence interval [CI], 0.18-0.46; $P < .001$); PFS was 5.2 versus 1.97 months (hazard ratio, 0.42; 95% CI, 0.32-0.57; $P < .001$); and ORR was 212.9% versus 5.7% (odds ratio, 4.9; 95% CI, 2.18-11.05; $P < .001$). **Conclusions:** This report presents the largest case series showing longer OS and PFS and better ORR when IRAEs occurred in a population of patients with advanced NSCLC treated with ICIs. The biological background for this phenomenon is being explored prospectively.

Clinical Lung Cancer, Vol. 20, No. 3, 201-7
Keywords: Immuno-related adverse events, Non-small cell lung cancer, Response, Survival

Introduction

Lung cancer, including 85% of non–small-cell lung cancer (NSCLC),[1] remains the most common cause of cancer-related death.[2]

New treatment options, such as immune checkpoint inhibitors (ICIs), are approved for the treatment of naive and relapsing advanced NSCLC. ICIs target and inhibit programmed cell death protein 1 on T cells (anti-PD-1) or its ligand (PD-L1) on tumor

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Submitted: May 11, 2018; Revised: Sep 21, 2018; Accepted: Oct 3, 2018; Epub: Oct 11, 2018

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1525-7304/$ - see frontmatter
https://doi.org/10.1016/j.cllc.2018.10.002

cells (anti-PD-L1) or on tumor microenvironment cells to enhance anti-tumor immunity.[3]

Until recently, ICIs have been primarily used for the second-line treatment of advanced NSCLC. To date, 3 drugs have been approved by the United States Food and Drug Administration based on 4 phase III clinical trials demonstrating the superiority of ICIs over standard docetaxel.[4-6] ICIs are now also registered in the first-line setting alone or in combination with chemotherapy as a result of the Keynote024 (phase III trial of pembrolizumab (MK-3475) vs platinum-based chemotherapy as first-line therapy for patients with metastatic non-small cell lung cancer (NSCLC) that expresses programmed cell death ligand 1) and 021G (Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study) trials.[5,7]

Releasing the brakes of the host-immune system, ICIs may alter the physiologic homeostasis of immune response, thus leading to the development of immune-related adverse events (IRAEs). A meta-analysis of the phase III Checkmate 017 (Nivolumab versus docetaxel in advanced squamous-cell non−small-cell lung cancer), Checkmate 057 (Nivolumab versus docetaxel in advanced non-squamous non−small-cell lung cancer), and Keynote 010 (Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial) studies was performed to assess the type and frequency of these IRAEs.[8] Adverse events of any grades based on the National Cancer Institute Common Terminology Criteria for Adverse Events occurred in 69% of patients, and adverse events grade 3 or higher occurred in 7% to 13% of patients.[9-11] The most frequent IRAEs exhibit endocrinopathy (hypothyroidism 4%-8%, hyperthyroidism 0%-5%), skin rashes (5%-11%), and hepatitis (2%-11%). The most severe were pneumonitis (3%-5%), colitis (1%-2%), hypophysitis (2%), and adrenal failure (0%-1%).

The development of new targeted therapies sometimes leads to new adverse events.[12,13] In a totally different context, these adverse events have been assessed as markers of treatment outcomes. This is the case for skin rash and tyrosine kinase inhibitors efficacy,[14] and we tried to find an analogy with ICIs and IRAEs.

A first trial published in November 2016 suggested a correlation between IRAEs and efficacy of ICIs in melanomas.[15]

To date, there is mainly 1 retrospective study with 134 patients[16] and 2 prospective studies with 38[17] and 43 patients,[18] all treated with nivolumab only, suggesting an association between the occurrence of IRAEs and the efficacy of ICIs in NSCLC.

The primary endpoint of this study was to assess the association between IRAEs and overall survival (OS) of patients with advanced NSCLC. Our secondary endpoints were to assess the association between IRAEs (type and severity) and progression-free survival (PFS), as well as the objective response rate (ORR) and disease control rate (DCR).

Materials and Methods

Patients

In this observational retrospective study, data from all patients older than 18 years of age who were diagnosed with metastatic NSCLC at 2 centers and who received at least 1 cycle of ICI (anti-PD-L1 or anti-PD-1) alone or in combination from April 2, 2013 to February 14, 2017 were analyzed. Patients known to have any previously controlled autoimmune disease were excluded.

Table 1 Baseline Characteristics

Characteristics	N	%
Median age, y (min-max)	61 (32-84)	
Gender		
Male	177	65.6
Female	93	34.4
Tobacco status		
Smoker/former smoker	239	88.5
Non-smoker	21	7.8
Brain metastases		
Yes	65	28.8
No	161	71.2
Performance status		
0-1	233	93.2
≥ 2	17	6.8
Mutation profile		
EGFR	3	1
KRAS	94	34.8
ALK rearrangement	3	1
BRAF	6	2.2
Immunotherapy type		
Anti-PD-1	241	89.3
Anti-PD-L1	29	10.7

Abbreviations: PD-1 = Programmed cell death protein 1; PD-L1 = programmed death-ligand 1.

Before the data collection, all patients provided signed informed consent allowing the use of data collected during standard care for research purposes. The Comité D'évaluation des Protocoles de Recherche Observationnels (reference CEPRO 2017-027) ethics committee approved this observational trial.

Data

Data were retrieved from electronic patient records. Clinical and epidemiologic data (age, gender, tobacco status, asbestos exposure), disease data (pathology, mutation status, stage), treatment data (type, treatment line, toxicity), and outcome data (response and survival) were collected.

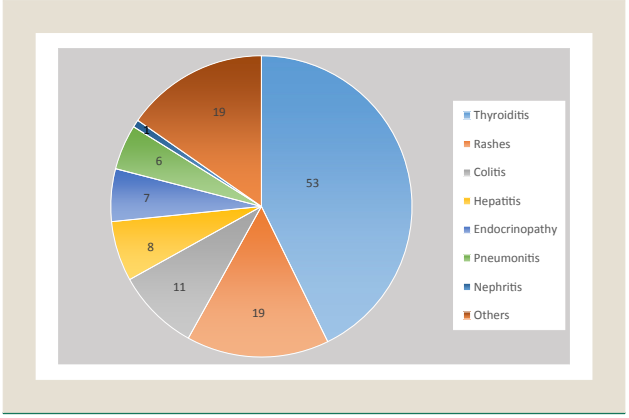
Toxicity was assessed as in pivotal trials, and as described in the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. The diagnosis and severity of IRAEs were based on clinical examinations and biological and imaging data.

Tumor response was assessed once every 2 months through computed tomography scans, according to the Response Evaluation Criteria in Solid Tumors, version 1.1.

Statistical Analysis

The primary endpoint was OS. The secondary endpoints were PFS, ORR, and DCR. OS was defined as the time from the beginning of immunotherapy to death from any cause, censored at

Figure 1 Distribution of Immune-Related Adverse Events in the Population (number of patients)



the date of last follow-up. PFS was defined as the time from the beginning of immunotherapy to documented disease progression or death from any cause, censored at the date of last follow-up. Medians were reported with interquartile range (IQR). As per Response Evaluation Criteria in Solid Tumors, version 1.1, the ORR included patients with partial or complete responses; DCR included partial responses, complete responses, and stable disease. To describe the population, we used effectives (numbers) and percentages for qualitative variables; means with standard deviation or medians with IQR for quantitative variables. To analyze OS and PFS, the Kaplan-Meier method was used to estimate the median survival with 95% confidence interval (CI) and Cox model to estimate hazard ratios (HRs) throughout groups' comparison with 95% CI. To assess IRAEs association with objective response rate, we used logistic regression analyses to estimate odds ratios (ORs) with 95% CIs throughout the group comparisons. Statistical analysis was performed using IBM SPSS Statistics for Windows, version 20.0 (IBM SPSS Inc., Chicago, IL).

Results

Patient and Disease Characteristics

Overall, 270 patients treated with ICIs were retrieved from our database and analyzed. Patient and disease characteristics are summarized in Table 1. The median age was 61 years (IQR, 32-84 years), and there were more men (65.6%) than women (34.4%). Most patients (88.5%; n = 239) were current or former smokers. The most frequent mutations (34.8%; n = 94) were the *KRAS* mutations. Regarding the treatments with ICIs, 89.3% (n = 241) of the patients received an anti-PD1 antibody; with 91.4% (n = 254) of patients being pretreated with chemotherapy prior to ICI.

Toxicity

Regarding ICI toxicity, 124 (44%) patients had an IRAE of any grade, with 53 (20%) cases of thyroid dysfunction, 19 (7%) rashes, 11 (4%) colitis cases, 8 (3%) hepatitis cases, 8 (2.9%) endocrine disorders, 6 (2%) pneumonitis cases, 1 nephritis case, and 19 (7%) other IRAEs (9 pruritus, 5 arthralgia, 1 multi-organ failure, 1 myocarditis, 1 myocardial ischemia, 1 psoriasis, 1 anaphylaxis) (Figure 1). We also analyzed the presence of IRAEs according to immunotherapy exposure. The analysis could be performed on 232 patients. Among patients with ICI exposure < 3 months, 33 (23%) patients had IRAEs, whereas 109 (77%) had no IRAE. Among patients with ICI exposure > 3 months, 47 (52%) patients had IRAEs, whereas 43 (48%) had no IRAE. For patients with more than 6 months exposure to ICIs, the rates were 54% with IRAEs versus 46% without IRAEs.

Outcome Analysis

For the entire studied population, the OS was 14 months, PFS was 2.6 months, ORR was 13%, and DCR was 51%.

We first compared the OS, PFS, ORR, and DCR for patient with IRAEs with those of patients without IRAEs. The median OS was longer for patients experiencing IRAEs (HR, 0.29; 95% CI, 0.18-0.46; $P < .001$). The median PFS was also longer for patients experiencing IRAEs (HR, 0.42; 95% CI, 0.32-0.57; $P < .001$) (Table 2, Figure 2). Finally, the ORR and DCR were significantly better for patients experiencing IRAEs compared with patients without any IRAE (22.9% vs. 5.7%, respectively; OR, 4.9; 95% CI, 2.18-11.05; $P < .001$, and 72.4% vs. 36.7%; OR, 4.52; 95% CI, 2.65-7.73; $P < .001$) (Table 2).

In terms of survival or response, the association between IRAE grade and ICI efficacy showed no statistically significant between-group differences for the different IRAE grades (Table 3).

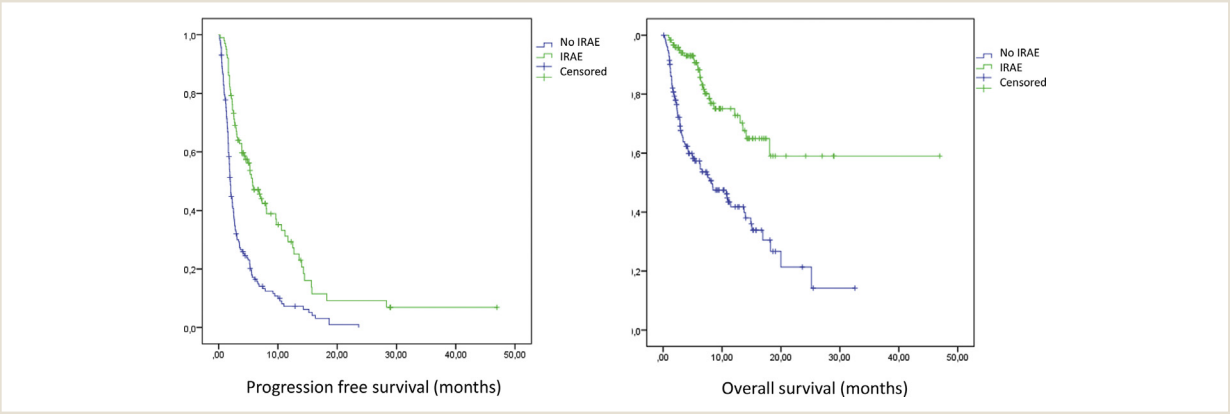
The median OS and median PFS differences according to the IRAE type were assessed (Table 4). For thyroid dysfunction, a statistically significant difference was observed. The median OS rate was not determined for patients with thyroid dysfunction; the median OS rate was 18.2 months for patients without thyroid dysfunction (HR, 0.46; 95% CI, 0.25-0.86; $P = .01$). Median PFS was 8.05 months for patients with thyroid dysfunction versus 2.59 months for patient without thyroid dysfunction (HR, 0.56; 95% CI, 0.39-0.85; $P = .005$). No statistically significant difference was found in the median OS and median PFS among patients with pneumonitis, colitis, hepatitis, and other endocrine disorders.

Table 2 Association Between IRAE Incidence and Immunotherapy Efficacy

	IRAE, n (%)	No IRAE, n (%)	*P* Value	HR/OR (95% CI)
ORR	24 (22.9)	9 (5.7)	<.0001	OR, 4.9 (2.18-11.05)
DCR	76 (72.4)	58 (36.7)	<.001	OR, 4.52 (2.65-7.73)
Median PFS, mos (IQR)	5.2 (3.7-6.88)	1.97 (1.79-2.16)	<.001	HR, 0.42 (0.32-0.57)
Median OS, mos (IQR)	–	8.21 (4.81-11.61)	<.001	HR, 0.29 (0.18-0.46)

Abbreviations: CI = Confidence interval; DCR = disease control rate; HR = hazard ratio; IQR = interquartile range; IRAE = immune-related adverse event; OR = odds ratio; ORR = objective response rate; OS = overall survival; PFS = progression-free survival.

Figure 2 Progression-free Survival and Overall Survival With Immune Checkpoint Inhibitors. Depending on the Incidence of IRAEs



Abbreviation: IRAE = Immune-related adverse event.

Finally, there was a trend towards longer OS when the onset of IRAEs was more than 3 months, with a median OS of 37.15 months versus 19.80 months when the onset of IRAEs was less than 3 months, without statistically significant difference (HR, 0.43; 95% CI, 0.14-1.26; $P = .123$) (Table 5). There was no difference in ORR (OR, 1.20; 95% CI, 0.44-3.29; $P = .73$).

Discussion

To the best of our knowledge, this study is the largest case series to assess the association between IRAEs and the efficacy of ICIs. Statistically significant differences were observed in the in OS, PFS, and ORR, in favor of the patients with IRAEs compared with the patients without any IRAEs. Subgroup analyses also showed better OS and PFS for patients with thyroid dysfunction.

The primary limitations of this trial are retrospective design and the low number of centers involved (2 centers). Another limitation could be the hypothesis that higher rate of IRAEs reflects higher treatment exposure and no T-cell activation. To define this point, we analyzed the number of IRAEs according to ICI exposure. The incidence of ORAEs was higher when ICI exposure was > 3 months than when ICI exposure was < 3 months. However, after 3 months of exposure, we found approximately the same rate of patients with (52%) and without (48%) IRAEs. This trend was confirmed above 6 months of exposure, with 54% patients with IRAEs and 46% without IRAE. These results suggest that higher rate of IRAEs does not reflect higher treatment exposure, suggesting higher OS and ORR are associated with IRAE occurrence more than ICI exposure. Furthermore (Table 5), we found no statistically significant difference in OS and ORR in patients who had IRAEs before 3 months and after 3 months. Patients with shorter ICIs exposure and earlier IRAEs did not have better outcomes. Prospective trials are needed to confirm these trends. One of them, published in December 2017,[18] enrolled 43 patients treated with nivolumab in Japan, and found a trend towards an association between ORR and PFS and the time from the first infusion of nivolumab to IRAE occurrence. The difference between these

Table 3 Association Between IRAE Grade and Immunotherapy Efficacy

	Grade 1, n (%)	Grade 2, n (%)	Grade 3, n (%)	Grade 4, n (%)
ORR	5 (17.2%)	5 (22.7%) $P = .67$ OR, 1.35 95% CI, 0.34-5.43	2 (14.3%) $P = .77$ OR, 0.77 95% CI, 0.13-4.56	0 (0%) $P = .99$
DCR	0 (71.4%)	11 (50%) $P = .13$ OR, 0.40 95% CI, 0.12-1.29	6 (43%) $P = .08$ OR, 0.3 95% CI, 0.08-1.1	4 (66.7%) $P = .81$ OR 0.8 95% CI, 0.12-5.27
Median PFS, mos (range)	5.75 (1.93-9.57)	3.05 (0.96-5.15) $P = .6$ HR, 1.17 95% CI, 0.64-2.17	2.07 (1.41-2.73) $P = .12$ HR, 1.73 95% CI, 0.87-3.44	1.87 (0.29-3.45) $P = .051$ HR, 2.66 95% CI, 0.99-7.09
Median OS, mos (range)	NR	14.09 (11.63-16.55) $P = .41$ HR, 1.60 95% CI, 0.51-4.98	6.24 (5.43-7.05) $P = .02$ HR, 3.88 95% CI, 1.23-12.29	19.97 (NA) $P = .63$ HR, 1.49 95% CI, 0.29-7.56

Abbreviations: CI = Confidence interval; DCR = disease control rate; HR = hazard ratio; IRAE = immune-related adverse event; NR = not reached; OR = odds ratio; ORR = overall response rate; OS = overall survival; PFS = progression-free survival.

Table 4 Association Between OS or PFS and IRAE Subtype

	PFS, mos (Range)	P Value	HR (95% CI)	OS, mos (Range)	P Value	HR (95% CI)
Pneumonitis						
Yes	2.66 (2.02-3.84)			6.24 (0-13.9)		
No	2.96 (1.68-4.5)	.68	1.19 [0.52-2.70]	19.97 (11.13-28.82)	.55	1.42 [0.45-4.54]
Colitis						
Yes	7.33 (4.10-10.54)			NR		
No	2.89 (2.19-3.59)	.39	0.73 [0.35-1.50]	18.2 (12.52-23.87)	.157	0.24 [0.03-1.73]
Hepatitis						
Yes	3.91 (1.79-6.03)			14.09 (1.17-27.02)		
No	2.89 (2.19-3.60)	.94	0.97 [0.45-2.08]	18.20 (12.56-23.86)	.95	0.97 [0.30-3.08]
Thyroiditis						
Yes	8.05 (3.33-14.58)			NR		
No	2.59 (2.15-3.04)	.005	0.58 [0.39-0.85]	18.2 (13.16-23.24)	.01	0.46 [0.25-0.86]

Abbreviations: CI = Confidence interval; HR = hazard ratio; IRAE = immune-related adverse event; NR = not reached; OS = overall survival; PFS = progression-free survival.

results and ours may be explained by the different population (Asian vs. Caucasian) and the type of IRAEs selected (mainly rashes, pyrexia, and diarrhea in the Japanese study).

The global efficacy of ICIs was consistent with the phase III pivotal trial results. In the overall population, the OS rate was 14 months versus 12.2 months in Checkmate 057,[10] 9.2 months in Checkmate 017,[9] 10.4 months and 12.7 months (for pembrolizumab 2 mg/kg and 10 mg/kg, respectively) in Keynote 010,[11] and 13.8 months in the OAK trial.[6] The PFS was 2.6 months in our study versus 2.3 months in Checkmate 057,[10] 3.5 months in Checkmate 017,[9] 3.9 months and 4 months in Keynote 010 for pembrolizumab 2 mg/kg and 10 mg/kg, respectively,[11] and 2.8 months in the OAK trial (Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial).[6] The ORR was 13% in our study versus 19% in Checkmate 057,[10] 20% in Checkmate 017,[9] 18% in Keynote 010,[11] and 14% in the OAK trial.[6] This difference in ORR could be observed because we analyzed a real-life population, in comparison with over-selected patients enrolled in clinical trials. Thereby, these results are interesting because they are relevant to everyday patients.

Adverse events were reported for 58% of patients in Checkmate 057,[10] 63% of patients treated with pembrolizumab 2 mg/kg and 66% of patients treated with pembrolizumab 10 mg/kg in Keynote 010,[11] and 64% of patients in OAK.[6] The toxicity rate was lower in the present study (46%) because only IRAEs were reported. The incidences of the different IRAEs were similar in the present study and the Keynote, Checkmate 057, Checkmate 017, and OAK trials. Thyroid dysfunction was observed in 13% to 19.5% of patients versus 19.6% in our study, and skin reactions were observed in 4% to 10% of patients versus 7% in our study. Pneumonitis occurred less frequently (2.2% vs. 5% to 5.8%) in our study. However, in a 2017 meta-analysis of 19 trials,[19] pneumonitis was reported in 3.6% of the patients receiving anti-PD-1 treatments and 1.3% of the patients receiving anti-PD-L1 treatments.

There is still a lack of data or conflicting results on how to predict the response to ICIs. A first retrospective trial published in September 2017 in JAMA[16] reported data from 134 patients treated with nivolumab. A total of 51% of patients had IRAEs, with a statistically significant longer PFS and OS in patients with IRAEs. However, no detail was given about IRAE definition and diagnosis. In a prospective trial published in Lung Cancer in 2018,[17] with 38 patients treated with nivolumab, a 30% incidence of IRAEs was found, with a better ORR for patients with IRAEs in comparison with patients without IRAEs (63% vs 7%). These 2 studies were performed in Asian patients, which could have a different toxicity profile for ICIs than for the Caucasian patients analyzed in our study. A retrospective analysis[20] of 160 patients with malignant diseases (including 44% [n = 71] of patients with NSCLC) reported IRAEs in 40% of patients. No difference was found for the OS rate in the overall population; however, 2 subgroups were analyzed separately: patients in clinical trials (46%; n = 73) and patients off trials (54%; n = 87). For the patients in clinical trials, the ORR was better for the patients with IRAEs compared with patients with no IRAE (P = .007). This difference was not observed in the subgroup of patients off-trial (P = .13). No significant difference in the OS rate was found between the subgroups (P = .827). Our population was larger and included only patients with NSCLC. Furthermore, in this study, the

Table 5 Association Between Time to Onset if IRAEs and Immunotherapy Efficacy

	Time to Onset of IRAEs < 3 Months	Time to Onset of IRAEs > 3 Months	HR/OR (95% CI)
OS, mos	19.80	37.15	HR 0.43 (0.14-1.26), P = .123
ORR, n (%)	16 (20.3)	7 (23.3)	OR, 1.20 (0.44-3.29), P = .73

Abbreviations: CI = Confidence interval; HR = hazard ratio; IRAEs = immune-related adverse events; N = number; OR = odds ratio; ORR = overall response rate; OS = overall survival.

analysis was based only on the first evaluation scan, whereas in our study, we chose to analyze the best response reached because we know that the ICI response can be delayed (the median time to response with nivolumab in NSCLC was 2.2 months, with a large range of 1.6-11.8 months in a phase III trial[9]). These factors could explain why we found a statistically significant difference when comparing patients with IRAEs with patients without any IRAE, whereas this difference was inconsistently found in previous case series or case reports.

In another publication[21] that reported 21% of thyroid dysfunction in 59 patients treated with pembrolizumab for NSCLC, the median delay of thyroid dysfunction diagnosis was 42 days, and the OS with pembrolizumab was significantly longer in subjects who developed thyroid dysfunction (HR, 0.29; 95% CI, 0.09-0.94; $P = .04$). A statistically significant difference was also found in our study when comparing patients with and without thyroid dysfunction. However, we could not show any difference in the OS or PFS for the other IRAE types, likely owing to the lack of patients in each group of IRAE. To our knowledge, no association between ICI outcomes and the occurrence of pneumonitis or other less frequently occurring IRAEs (eg, colitis, hepatitis, and other endocrine dysfunctions) has been reported in the literature.

Previous studies have reported that the ORR of ICI in NSCLC is 14.6% to 20%,[4,10,11,19,22,23] and up to 80% of patients have no response to ICIs. However, we do not know how to identify these patients.

We demonstrated a statistically significant association between IRAEs and ORR. The occurrence of IRAEs could be used to predict what the future response to treatment might be. The association between IRAEs and the efficacy of ICIs highlights the need for the better diagnosis and management of IRAEs to be able to continue ICIs as long as possible, despite the IRAEs. It could also be an additional argument in favor of pseudo-progression in doubtful situations when the diagnosis between disease progression and pseudo-progression is difficult. Our study suggested a significant association between the efficacy of ICIs and the incidence of IRAEs, particularly for thyroid dysfunction. The occurrence of IRAEs may be owing to the strongest T cell activation. Further prospective studies are needed to understand the underlying mechanisms and to correlate the duration of efficacy with the duration or severity of IRAEs, as well as the effect of ICIs discontinuation on response and survival in case of severe IRAEs. We need further prospective trials with larger cohorts to assess the association between ICI efficacy and less frequent IRAEs (ie, pneumonitis, hepatitis, colitis, cutaneous adverse events). We also need longer patient follow-up periods after ICIs stop to determine whether the response duration is longer for patients with IRAEs than for those without them, even if the treatment is stopped.

Clinical Practice Points

- ICIs are widely used for the treatment of advanced NSCLC. They are responsible for IRAEs, and all organs can be involved. We already have data regarding IRAE frequency, severity, and guidelines on IRAE management. However, data are missing regarding the prognostic role of IRAEs and their association with ICI outcomes.
- The new finding of this study is a statistically significant association between IRAE occurrence and ICI efficacy, with a longer OS, longer PFS, better ORR, and better DCR for patients with IRAEs. Furthermore, this is the largest case series on the subject.
- In the foreseeable future, the appearance of IRAEs could help physicians to detect patients with good response to ICIs. The occurrence of IRAEs could also be helpful to differentiate real progression and pseudo-progression in doubtful situations.

Disclosure

The authors have stated that they have no conflicts of interest.

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