Lung Cancer 115 (2018) 71–74

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Short communication

Correlation between immune-related adverse events and efficacy in non-small cell lung cancer treated with nivolumab

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ARTICLE INFO

Keywords:
Non-small-cell lung cancer (NSCLC)
Nivolumab
Immune-related adverse events (irAEs)

ABSTRACT

Objectives: Patients treated with nivolumab often experience its unique adverse events, called immune-related adverse events (irAEs). Regarding the mechanisms of immune-checkpoint inhibitors (ICIs), the occurrence of irAEs may also reflect antitumor responses. Here, we report the clinical correlation between irAEs and efficacy in NSCLC patients treated with nivolumab.

Materials and methods: Between December 2015 and February 2017, 38 advanced NSCLC patients were treated in our institution. All the patients were enrolled in our single-institutional, prospective, observational cohort study (UMIN000024414). IrAEs were defined as having a potential immunological basis that required more frequent monitoring and potential intervention. We divided the patients into two groups (irAEs group or no-irAEs group) and evaluated the objective response rate (ORR) and progression-free survival (PFS).

Results: The median age of the patients was 68.5 years (range 49–86 years); male/female ratio was 28/10; squamous/non-squamous cell carcinoma cases were 10/28; performance status was 0–1/2/3, 7/26/5. Among the overall population, ORR was 23.7% and median PFS was 91 days. At the data cutoff, 14 irAEs were observed. The most common irAE was interstitial pneumonia (n = 5). Other irAEs were hypothyroidism (n = 4), hyperthyroidism, hypopituitarism, liver dysfunction, rash, and elevated thyroid stimulating hormone levels (n = 1, each). Patients with irAEs had significantly higher ORRs compared with no-irAE patients (63.6% versus 7.4%, $p < 0.01$). Similarly, the PFS among irAE patients was longer (median: not reached [95% confidence interval {CI}: 91 days to not applicable]) than no-irAE patients (median 49 days [95% CI: 36–127 days], hazard ratio [HR] 0.10 [95% CI: 0.02–0.37, $p < 0.001$]). Landmark analysis of patients who achieved PFS ≥60 days demonstrated similar tendencies, but this was not significant (HR 0.28 [95% CI: 0.04–1.46], p = 0.13).

Conclusion: There was a correlation between irAE and efficacy in NSCLC patients treated with nivolumab.

1. Introduction

Immune-checkpoint inhibitors (ICIs) have been established as novel standard treatment for various types of malignancies including non-small cell lung cancer (NSCLC). In pivotal phase III trials, nivolumab, the first-in-class ICI, demonstrated prolongation of overall survival (OS) compared with docetaxel in patients with previously treated NSCLC [1,2]. Pembrolizumab, another anti-programmed death-1 (PD-1) inhibitor, demonstrated outstanding efficacy results for both progression-free survival (PFS) and OS compared with platinum-doublet chemotherapy in chemo-naïve NSCLC patients with strongly positive expression of tumor program-death ligand 1 [3]. On the other hand, patients treated with ICIs sometimes experience their unique adverse events, called immune-related adverse events (irAEs). Thyroid dysfunction and gastrointestinal toxicity are common types of irAEs, and they are rarely, but critically manifested in interstitial lung disease, type I diabetes, or hypophysitis. Recently, its patterns and prevalence have been reported [4], but several clinical questions about irAEs remain. Regarding the mechanisms of ICIs, the occurrence of irAEs may also reflect antitumor responses. Among melanoma patients treated with ICIs, one report suggested that patients who exhibited irAEs demonstrated higher antitumor responses, but in another report, there was no correlation [5,6]. Recently, nivolumab and pembrolizumab have been approved for NSCLC in Japan; this correlation has not been

Abbreviations: irAE, immune related adverse event; ECOG PS, European cooperative oncology group performance status; n.s., not significant; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; PD-L1, programmed death-ligand 1; TKI, tyrosine-kinase inhibitor

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https://doi.org/10.1016/j.lungcan.2017.11.019
Received 28 August 2017; Received in revised form 7 November 2017; Accepted 20 November 2017

Table 1
Baseline characteristics.

Characteristics	Overall (n = 38)		irAE group (n = 11)		No-irAE group (n = 27)		P value
Age (years)							n.s.
Median (range)	68.5 (49-86)		73 (54-86)		68 (49-83)		
Sex (n (%))							n.s.
Male	28	(74)	9	(82)	19	(70)	
Female	10	(26)	2	(18)	8	(30)	
Smoking status (n (%))							n.s.
Non-, or light smoker	12	(32)	3	(27)	9	(33)	
Heavy smoker	26	(68)	8	(73)	18	(67)	
ECOG PS (n (%))							n.s.
0	7	(19)	1	(9)	6	(22)	
1	26	(68)	8	(73)	18	(67)	
≥ 2	5	(13)	2	(18)	3	(11)	
Clinical stage (n (%))							n.s.
IIIB	7	(18)	3	(27)	4	(15)	
IV	22	(58)	6	(55)	16	(59)	
Postoperative relapse	9	(24)	2	(18)	7	(26)	
Histopathology (n (%))							n.s.
Squamous	10	(26)	4	(36)	6	(22)	
Non-squamous	28	(74)	7	(64)	21	(78)	
EGFR mutation	6		1		5		
ALK fusion	1		0		1		
PD-L1 expression (n (%))							n.s.
≥ 50%	13	(34)	6	(55)	7	(26)	
1-49%	20	(53)	3	(27)	17	(63)	
0%	5	(13)	2	(18)	3	(11)	
Prior systemic therapy (total n)							n.s.
Platinum doublet	35		10		25		
Monotherapy	18		9		9		
TKI	7		1		6		

Abbreviations:
irAE, immune-related adverse event; ECOG PS, European cooperative oncology group performance status; n.s., not significant; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; PD-L1, programmed death-ligand 1, TKI, tyrosine-kinase inhibitor

fully investigated. Here, we conducted a preliminary analysis to elucidate the correlation between irAEs and efficacy in NSCLC patients treated with nivolumab.

2. Materials and methods

Between December 2015 and February 2017, 38 advanced NSCLC patients were treated with nivolumab (3 mg/kg, every 2 weeks), and were enrolled in our single-institutional, prospective, observational cohort study (UMIN000024414). Informed consent was obtained from all the patients. In this study, responses were evaluated using the Response Evaluation Criteria for Solid Tumors (RECIST) ver. 1.1. by chest computed tomography and/or brain magnetic resonance imaging (MRI) every 6–8 weeks. PFS was assessed from the first day of treatment with nivolumab to the earliest signs of disease progression or death from any cause. Toxicity was followed by Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. IrAEs were defined as having a potential immunological basis that required more frequent monitoring and potential intervention with immune suppression and/or endocrine replacement therapy, which was previously mentioned by Weber et al. [4]. Based on this, we divided patients into two groups (irAE group and no-irAE group), and subsequently evaluated the overall