Value of non-specific signal symptoms (SSs) as a prodrome of immune-related adverse events: consecutive analysis of 200 patients with non-small cell lung cancer receiving nivolumab

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INTRODUCTION: Immune-related adverse events (irAEs) are sometimes fatal problems, however detection at an early stage is difficult.
Objectives: We examined the significance of non-specific symptoms as a prodrome of irAEs in patients with non-small cell lung cancer (NSCLC).
METHODS: We reviewed consecutive patients who received nivolumab (NIVO) for metastatic NSCLC between December 2015 and August 2017. NIVO was administered at a dose of 3 mg/kg every two weeks. We recorded the patient demographics, irAEs, and signal symptoms (SSs). Non-specific symptoms (fever, fatigue and headache) occurring 7 days or earlier before the onset of specific irAEs were considered as SSs. The associations between clinical information, including SSs before irAEs, were evaluated statistically using the Fisher exact test and logistic regression.
RESULTS: A total of 200 patients received NIVO. Among them, 131 (65%) were male, the median age was 63 years (range, 30-83 years), 27 (14%) had a PS of 2 or more, 144 (72%) were smokers, and 48 (24%) had squamous NSCLC. SSs occurred in 37 of the 58 patients who experienced irAEs. The SSs occurred a median of 19 days (range, 7-154 days) before the subsequent irAEs. The SSs were positively associated with the irAEs (P < 0.01, Fisher exact test). A logistic regression analysis showed that the occurrence of the irAEs was significantly higher in male (odds ratio [OR]; 5.70, 95% C.I.; 2.03-16.0) and patients who experienced SSs (OR; 19.8, 95% C.I.; 7.47-52.5).
CONCLUSION: SSs might play an important role in the early detection of irAEs in patients receiving immune-checkpoint blockade therapy.

Patients and Method

- Consecutive patients with cytological or histological confirmed advanced / metastatic NSCLC who received NIVO at dose of 3 mg/kg every two weeks were eligible for analysis.
- The patient characteristics, including age, sex, Eastern Cooperative Oncology Group performance status (PS), smoking history, tumor histology, driver gene alteration, and information about signal symptoms and irAEs were collected.
- **Non-specific symptoms (fever, fatigue and headache) occurring 7 days or earlier before the onset of specific irAEs were considered as SSs.**
- **SSs were collected using an uniform interview form by medical professionals at every visit before administration of NIVO.**
- IrAEs were assumed to be immune-related and were reported by a single investigator using the of Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. **Two other professionals independently reviewed the findings.**

Patient characteristics

	N=200	% or range
Age (median)	63	30-83
Female / Male	69/131	35/65
PS 0-1 / 2-3	173/27	86/14
Smoking history		
Smoker (past or current)	144	72
Never smoker	56	28
Tumor histology		
Non-squamous	152	76
Squamous	48	24
Driver gene alternation		
Positive (EGFR or other)	36	18
Negative	164	82
Treatment line of NIVO		
2	83	41.5
3 or more	115	57.5
Signal symptoms (SSs)	37	19
Fever	20	10
Fatigue	24	12
Headache	3	2
Days after 1 st NIVO when SSs appeared	19	7-154
Year of treatment initiation		
2015-2016	176	88
2017-	24	12

Relationship between SSs and irAEs

		irAEs		
		Yes	No	Total
SSs	Yes	30	7	37
	No	29	134	163
	Total	59	141	200

➤ Odds ratio 19.8 (95%C.I. 7.9-49.5), Fisher’s exact test, p<0.01

Frequency of irAEs

irAEs (N=59)	Any grade	Grade 1	Grade 2	Grade 3	Grade 4
Interstitial pneumonia	15	1	3	7	4
Thyroid dysfunction	16	4	11	0	1
Diarrhea, colitis	12	2	3	5	2
Adrenal dysfunction	4	0	1	3	0
Dermatitis	10	6	4	0	0
Acute kidney injury	2	0	0	2	0
Other	4	0	1	2	1

Number of SSs and frequency of irAEs

Number of SSs	N	With irAEs N=59	Without irAEs N=141
0	163	29	134
1	29	23	6
2	7	6	1
3	1	1	0

Multivariate analysis (Logistic regression)

	n	OR	95% C.I.	p value
Age				
≥ 70	46	1		
< 70	154	1.25	0.50-3.13	0.626
Sex				
Female	69	1		
Male	131	5.70	2.03-16.0	0.001
PS				
2-3	27	1		
0-1	173	2.19	0.60-8.04	0.237
Smoking history				
Never smoker	56	1		
Smoker	144	1.01	0.42-2.39	0.988
Histology				
Non-squamous	152	1		
Squamous	48	0.96	0.39-2.33	0.923
Driver gene alteration				
Negative	164	1		
Positive	36	2.28	0.71-7.29	0.165
Year of treatment initiation				
2015-2016	176	1		
2017-	24	1.32	0.39-4.53	0.656
SSs				
No	163	1		
Yes	37	19.8	7.47-52.5	<0.001

Conclusion

➤ SSs might play an important role in the early detection of irAEs in patients receiving immune-checkpoint blockade therapy.

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