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The association between tumor burden and severe immune-related adverse events in non-small cell lung cancer patients responding to immune-checkpoint inhibitor treatment

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ABSTRACT

Objectives: The use of immune checkpoint inhibitors (ICIs) for advanced non-small cell lung cancer (NSCLC) has demonstrated survival benefits, although some treatment responders (defined as patients with non-progressive disease) are forced to discontinue treatment because of severe immune-related adverse events (irAEs). An association between treatment efficacy and irAEs has been reported. However, it is unclear which treatment responders are likely to develop severe irAEs. We aimed to examine risk factors for ICI-related severe irAEs in patients with NSCLC.

Materials and methods: Between February 2016 and October 2018, we retrospectively evaluated 42 patients with NSCLC at our institution who responded to ICI treatment. Tumor burden was measured as the sum of the unidimensional diameters of up to five target lesions, according to the Response Evaluation Criteria in Solid Tumors version 1.1.

Results: ICIs were discontinued in 15 of 42 treatment responders because of severe irAEs. Tumor burden was a significant independent predictor of severe irAEs ($p = 0.03$). The odds ratio of severe irAEs and tumor burden over 90 mm was 8.62 (95% confidence interval = 1.96–37.9, $p = 0.004$).

Conclusion: A high tumor burden was a risk factor for severe irAEs in patients with NSCLC who responded to ICI treatment.

1. Introduction

Immune checkpoint inhibitors (ICIs), specifically programmed cell death 1 (PD-1)/PD-1 ligand (PD-L1) inhibitors, have impressive efficacy against advanced non-small cell lung cancer (NSCLC) [1]. Some predictive biomarkers for evaluating the response to ICIs have previously been reported [2]. Additionally, previous studies have shown positive associations between immune-related adverse events (irAEs) and ICI efficacy [3]. However, no studies have determined which treatment responders are likely to develop severe irAEs. Several studies have identified risk factors for pneumonitis in NSCLC patients receiving ICIs [4]. To our knowledge, an association between baseline tumor burden and serious irAEs has not yet been studied in NSCLC patients. Therefore, we aimed to evaluate risk factors for ICI-related severe irAEs, with a focus on tumor burden.

2. Materials and methods

We identified advanced NSCLC patients who received ICIs between February 2016 and September 2018 through searching our hospital's prescription drug database. All patients were followed up until the end of October 2018. The following variables were collated for the investigation: age, sex, Eastern Cooperative Oncology Group performance status, smoking status, histology, stage, PD-L1 expression, treatment

Abbreviations: CI, confidence interval; CR, complete response; ICI, immune checkpoint inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status; irAE, immune-related adverse event; NSCLC, non-small cell lung cancer; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; PR, partial response RECIST Response Evaluation Criteria in Solid Tumors; ROC, receiver operating characteristic; SD, stable disease

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line, type of ICI, treatment response, and tumor burden. The treatment response was determined based on the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v.1.1). We defined treatment responders as patients with non-progressive disease, and we defined severe irAEs as toxicities related to ICI therapy (grade ≥3 according to the Common Terminology Criteria for Adverse Events version 5.0) or adverse effects after which physicians considered treatment continuation impossible. According to a previous study, we measured baseline tumor burden using computed tomography or magnetic resonance imaging according to RECIST v.1.1, and tumor burden was defined as the sum of the longest diameters for a maximum of five target lesions and up to two lesions per organ [5]. PD-L1 expression was determined according to SRL, Inc. using the Dako PD-L1 IHC 22C3 PharmDx test [6].

Comparisons between groups were performed using the Mann-Whitney *U* test for continuous variables and Fisher's exact tests for categorical variables. The optimal cutoff level for tumor burden was determined using a receiver operating characteristic (ROC) analysis. Odds ratios were evaluated using the chi-squared test. A p-value of < 0.05 was considered statistically significant. All statistical analyses were conducted using EZR, a graphical user interface for R software [7].

3. Results

We identified 78 patients who had received ICI treatment for advanced NSCLC; however, 32 patients were excluded because of disease progression. In addition, we excluded 4 patients in whom lesions could not be measured. Thus, 42 treatment responders who had received ICI were included in this study (Supplemental Fig. 1). The characteristics of the 42 patients are summarized in Table 1. There were 30 patients with any grade of irAE, 20 of 30 patients had multiple irAEs, and 15 patients developed severe irAEs (Supplemental Table 1).

A significant difference in tumor burden was observed between patients with severe irAEs and those without severe irAEs (p = 0.03) (Table 1). A ROC analysis indicated that 90 mm was the optimal cutoff level for tumor burden (sensitivity = 85.2%, specificity = 60%, area under the curve = 0.7, 95% confidence interval [CI] = 0.53–0.87]). Only high tumor burden showed a correlation with the onset of severe irAEs (Table 2). The odds ratio of severe irAEs and high tumor burden was 8.62 (95% CI = 1.96–37.9, p = 0.004).

4. Discussion

This study investigated the risk factors for the development of severe irAEs in NSCLC patients who had been treated with ICIs. Our findings suggest that tumor burden is related to the onset of severe irAEs.

A recent retrospective cohort study indicated that real-world patients were more likely to develop severe irAEs than patients participating in clinical trials [8]. Therefore, investigating the risk factors for developing severe irAEs is important; however, other than pneumonitis, such risk factors have not been elucidated [4]. There have been reports regarding the relationship between tumor burden and poor ICI efficacy [5,9]; however, in practical settings, treatment responders have a high tumor burden and often develop various severe irAEs. Therefore, in this study, we investigated treatment responders with high tumor burdens. A previous study concerning head and neck squamous cell carcinoma indicated an association between treatment response and severe irAEs [10]; however, determining which patients are likely to respond best to ICIs is vital. Therefore, identifying risk factors prior to initiating treatment is important. To our knowledge, our study is the first to report an association between baseline tumor burden and severe irAEs. One previous study demonstrated that pretreatment tumor size determined the strength of the drug-induced T-cell response required to shrink a patient's tumor: the larger the tumor, the stronger the required drug-induced T-cell response [9]. According to these results, we assumed that treatment responders with high tumor burdens would have strong immunological reactions. This may be immunologically plausible and could explain why treatment responders with larger tumors are more likely to develop severe irAEs.

There were some limitations to this study. First, this was a retrospective study using clinical records from a single institution, with a small sample size. Our results need to be validated in larger trials. However, our findings suggest that patients with high tumor burdens should be carefully followed up for serious irAEs. Second, the follow-up period in this study was short and late-onset severe irAEs may have been overlooked, although one previous study showed that severe irAEs were likely to develop relatively early in the treatment course [8]. Third, this study only included treatment responders, which may have resulted in selection bias. However, few patients with disease progression develop severe irAEs. It appears that disease activity exceeds the immune response for tumor reduction. Therefore, we recommend being

Table 1
Patient Characteristics.

	Total (%) (n = 42)	Patients with severe irAEs (%) (n = 15)	Patients without severe irAEs (%) (n = 27)	p-value
Age (years)				
Median (range)	69 (42–81)	69 (63–76)	69 (42–81)	0.54
Sex				
Male	33 (79)	12 (80)	21 (78)	> 0.99
Female	9 (21)	3 (20)	6 (22)	
ECOG PS				
0	19 (45)	7 (47)	12 (44)	0.56
1	20 (48)	6 (40)	14 (52)	
2	3 (7)	2 (13)	1 (4)	
Smoking status				
Never	7 (17)	2 (13)	5 (19)	> 0.99
Current or former	35 (83)	13 (87)	22 (81)	
Histology				
Adenocarcinoma	30 (71)	8 (53)	22 (81)	0.1
Squamous	7 (17)	5 (33)	2 (7)	
Other	5 (12)	2 (13)	3 (11)	
Stage				
II	2 (5)	0 (0)	2 (7)	0.83
III	9 (21)	4 (27)	5 (19)	
IV	24 (57)	9 (60)	15 (56)	
Recurrent	7 (17)	2 (13)	5 (19)	
PD-L1 expression				
≥50%	27 (64)	12 (80)	15 (56)	0.36
< 50%	9 (21)	2 (13)	7 (26)	
Unknown	6 (14)	1 (7)	5 (19)	
Treatment line				
First	16 (38)	7 (47)	9 (33)	0.6
Second	17 (40)	6 (40)	11 (41)	
Third and higher	9 (21)	2 (13)	7 (26)	
Drug				
Nivolumab	12 (29)	3 (20)	9 (33)	0.25
Pembrolizumab	27 (64)	12 (80)	15 (56)	
Atezolizumab	3 (7)	0	3 (11)	
Response				
Complete response	1 (2)	0	1 (4)	0.83
Partial response	25 (60)	10 (67)	15 (56)	
Stable disease	16 (38)	5 (33)	10 (37)	
Tumor burden (mm)				
Median (range)	58 (15–232)	93 (23–232)	52 (15–176)	0.03

irAEs, immune-related adverse events; ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed cell death ligand 1.
irAEs, immune-related adverse events; ECOG PS, Eastern Cooperative Oncology Group performance status; CR, complete response; PR, partial response; SD, stable disease; PD-L1, programmed cell death ligand 1.

Table 2
Risk factors for severe immune-related adverse events.

Variable	Patients with severe irAEs (n = 15)	Patients without severe irAEs (n = 27)	p-value
Age ≥75 years	2	5	> 0.99
Male sex	12	21	> 0.99
ECOG PS ≥1	8	15	> 0.99
Current/former smoker	13	22	> 0.99
PD-L1 expression ≥50%	12	15	0.36
First-line treatment	7	9	0.51
Treatment response (CR/PR)	10	16	0.75
Tumor burden ≥90 mm	9	4	0.005

irAE, immune-related adverse event; ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed cell death ligand 1; CR, complete response; PR, partial response.
Data are presented as n.
irAEs, immune-related adverse events; ECOG PS, Eastern Cooperative Oncology Group performance status; CR, complete response; PR, partial response; PD-L1, programmed cell death ligand 1.

particularly attentive to severe irAEs for treatment responders. However, selection bias may have been a factor in our study, and further studies are needed to confirm our results.

In conclusion, we demonstrated an association between tumor burden and serious irAEs. Patients with high tumor burden require special care with respect to not only disease progression but also to severe irAEs during treatment with ICIs.'

Informed consent

This study was approved by the institutional review board of our institution, and all patients provided written informed consent. Research was conducted in accordance with the 1964 Declaration of Helsinki and its later amendments.

Conflict of interest statement

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2019.02.011.

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