Correlation Between Immune-related Adverse Events and Therapeutic Effects of Nivolumab in Patients With Malignant Pleural Mesothelioma

Hiroto Yoneda
Tokushima University
Hiroshi Nokihara
Tokushima University
Atsushi Mitsuhashi
Tokushima University
Ryohiko Ozaki
Tokushima University
Yohei Yabuki
Tokushima University
Hirokazu Ogino
Tokushima University
Kenji Otsuka
Tokushima University
Yasuhiko Nishioka (yasuhiko@tokushima-u.ac.jp)
Tokushima University

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Abstract

Background:

Nivolumab is used for the treatment of malignant pleural mesothelioma (MPM). However, immune-related adverse events (irAEs) occur in patients treated with nivolumab. Several studies have reported the correlation between irAEs and therapeutic effects of immune checkpoint inhibitor, but none have reported the correlation in MPM. Here we report a retrospective study which shows the correlation between irAEs and therapeutic effects of nivolumab in patients with MPM.

Methods:

This study included patients treated with nivolumab at Tokushima University Hospital from February 2009 to December 2019. We retrospectively reviewed the medical records to evaluate the several clinical factors, such as the presence or absence of irAEs, their severities, progression-free survival (PFS), overall survival (OS) or objective response to the treatment.

Results:

Eight patients received treatment with nivolumab. Overall response rate was 14.3% and the disease control rate was 87.5%. Median PFS was 6.6 months (95% confidence interval, 2.4 to 10.8 months) and median OS was 15.2 months (95% confidence interval, 11.1 to 19.4 months). IrAEs occurred in six patients (85.7%), and grade 2 ≤ irAEs occurred in four patients (50.0%). Median PFS was significantly longer in the grade 2 ≤ irAEs group (16.3 months) than in their counterpart (3.8 months; p = 0.0266).

Conclusions:

This is the first study to report the correlation between irAEs and therapeutic effects in patients with MPM. Because the presence of irAEs may be associated with a favorable clinical outcome, early detection and appropriate management of irAEs will increase the therapeutic benefits to patients.

Background

Malignant pleural mesothelioma (MPM) is a rare tumor, but it is an aggressive tumor and has a poor prognosis. The median overall survival is reported to be approximately seven months without any treatments,[1] and it is also reported to be 6 to 18 months even with the appropriate treatments, regardless of the therapeutic modalities.[2–4] Many patients with MPM are not offered surgery due to advanced stage, old age, comorbidities, or poor performance status, and are instead considered to be palliative chemotherapy. The combination of cisplatin and pemetrexed is a standard first-line treatment for unresectable MPM.[5] Nivolumab, an anti-programmed cell death protein 1 (PD-1) antibody, has showed an encouraging clinical benefits as a second- or third- line treatment,[6,7] and has been approved in Japan since 2018.

The treatment with nivolumab may lead to immune-related adverse events (irAEs), which sometimes results in the interruption or discontinuation of the treatment.[8] Previous reports in melanoma, non–small-cell lung cancer, and gastric cancer patients have shown that the presence of irAEs with nivolumab were positively associated with their progression-free survival (PFS) and overall survival (OS).[9–13] However, the correlation between irAEs and outcome of nivolumab for patients with MPM is still unknown. As such, we conducted the retrospective study to investigate whether irAEs are associated with clinical efficacies of nivolumab in MPM.

Methods

Participants

Patients, who were diagnosed as MPM in the Department of Respiratory Medicine and Rheumatology at Tokushima University Hospital from February 1st, 2009 to December 31th, 2019, were retrospectively analyzed. Twenty-two patients were diagnosed with MPM (Fig. 1). Three patients received best supportive care alone, and 19 patients received chemotherapy. 14 of 19 patients received two or more regimens, and eight patients were treated with nivolumab, and we analyzed these eight patients in this study. This study was performed in accordance with the Declaration of Helsinki and was approved by the Institutional review board.

Data collection

We examined several clinical factors including age, gender, Eastern Cooperative Oncology Group (ECOG) performance status (PS), histology, clinical stage, presence or absence of irAEs, the severities of irAEs, PFS, OS and objective response to the treatment. The data were collected retrospectively from the medical records in our hospital.

Treatment and assessment

Nivolumab was administered intravenously at a dose of 240 mg/body every two weeks. Nivolumab was administered until disease progression or unacceptable adverse events. Adverse events were assessed according to the National Cancer Institute-Common Toxicity Criteria for Adverse Events (NCI-CTCAE) version 5.0. Clinical responses to the treatment were categorized as either complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Overall response rate (ORR) was defined as the proportion of CR and PR, and disease control rate (DCR) was defined as that of CR, PR and SD. PFS was defined as the period from the start of treatment with nivolumab to the date of disease progression. OS was defined as the period from the start of treatment with nivolumab to death or loss of follow-up.

Statistical analysis

PFS and OS were estimated by the Kaplan-Meier method, and their statistical differences were analyzed by the Log-rank test. The statistical analyses were performed using GraphPad Prism version 7 (GraphPad

Software, La Jolla, California USA). In this analysis, a *p*-value of < 0.05 was considered to indicate a significant difference.

Results

Patient characteristics

Patient characteristics are shown in Table 1. Among the total eight patients, five patients (62.5%) were male and three patients (37.5%) were female, and median age was 73.0 (56–84) years. Six of eight patients (75.0%) have asbestos inhalation history. All patients were histologically epithelial type. All patients received a combination chemotherapy of platinum (three received cisplatin and five received carboplatin) and pemetrexed as a first-line treatment. Seven patients received nivolumab as a second-line and one received as a third-line treatment.

Table 1
Patient characteristics

No. of patients	**8**	
Gender (%)		
Male	5	(62.5)
Female	3	(37.5)
Age (years)		
Median (range)	73	(56–84)
ECOG performance status (%)		
0	4	(50.0)
1	3	(37.5)
2	1	(12.5)
Smoking status (%)		
Never	3	(37.5)
Ex/current	5	(62.5)
Asbestos inhalation history (%)		
+	6	(75.0)
-	2	(25.0)
Histology (%)		
Epithelial type	8	(100.0)
1st line regimen		
CDDP + PEM	3	(37.5)
CBDCA + PEM	5	(62.5)
Regimen line (%)		
2nd	7	(87.5)
3rd	1	(12.5)
Abbreviations: CDDP, cisplatin; PEM, pemetrexed; CBDCA, carboplatin		

Effects of nivolumab in previously treated MPM patients.

Regarding the best overall response, PR was 12.5%, SD was 75.0%, and PD was 12.5%. The ORR was 12.5% and the DCR was 87.5% (Table 2). Median follow-up time was 14.8 months. Median PFS was 6.6 months (95% confidence interval [CI], 2.4 to 10.8 months) and median OS was 15.2months (95% CI, 11.1 to 19.4 months) (Fig. 2).

Table 2
Anti-tumor effect of nivolumab in previously treated malignant pleural mesothelioma patients

No. of patients	**8**	
Best overall response (%)		
CR	0	(0.0)
PR	1	(12.5)
SD	6	(75.0)
PD	1	(12.5)
ORR	12.5%	
DCR	87.5%	
Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate		

Onset of irAEs.

The irAEs were observed in total six patients (75.0%), and grade 2 ≤ irAEs were obseved in four patients (50.0%) (Table 3). The two patients with grade 2 or 3 pneumonitis needed to be treated with corticosteroids and a patient with grade 3 hypophysitis received the corticosteroids replacement therapy. The symptoms of these patients with grade 2 ≤ irAEs have been improved by the treatments, but treatments with nivolumab were discontinued. No irAEs-related death was observed in this cohort.

Table 3
Immune-related adverse events (irAEs)

	Total	%	Grade 1	Grade 2≤
No. of irAE patients	6	75.0		
IrAE event (total)	7		2	5
Infusion reaction	1	12.5	1	0
Itching	1	12.5	1	0
Hypothyroidism	2	25.0	0	2
Pneumonitis	2	25.0	0	2
Hypophysitis	1	12.0	0	1

Correlation between irAEs and therapeutic effects

We next examined the correlation between irAEs and therapeutic effects in patients with MPM treated with nivolumab. We analyzed the therapeutic effects separately for the patients with grade 2 > irAEs or without irAEs (n = 4) and the patients with grade 2 ≤ irAEs (n = 4). Median PFS was significantly longer in the grade 2 ≤ irAEs group (16.3 months) than in the grade 2 > irAEs group (3.8 months; p = 0.0266; Fig. 3).

Discussion

Nivolumab has been shown to be effective as a second-line treatment of MPM, and the ORR, PFS, and OS were reported to be 24–29%, 2.6–6.1 months, and 17.3 months, respectively.[6,7] The treatment effects in the current study were similar to previous reports. In terms of the adverse events, there is a report showing that 32.4% of patients treated with nivolumab in the second line had treatment-related adverse events of grade 3 or higher.[7] Our study also showed that treatment-related adverse events of grade 3 or higher were observed in two patients (25.0%), which was less frequent than the previously report, though the number of patients was small.

Programmed death-ligand 1 (PD-L1) expression in lung cancer[14,15] and microsatellite instability-high (MSI-H) in colorectal cancer[16] are used to predict the therapeutic effects of immune checkpoint inhibitors (ICIs). Among MPM patients, the PD-L1 expression was reported to be negative, positive, and highly positive in 58.2, 41.8, and 9.6% of the patients, and the high PD-L1 expression was associated with worse OS.[17] In another report, two patients were identified as MSI-H among 83 MPM patients[18], however, the correlation between MSI-H and the therapeutic effects of ICIs in MPM is still unclear. Matsuoka H, et al recently analyzed a cohort with various types of cancer including MPM, and showed that ORR, OS and PFS were significantly better in the patients with irAEs than in those without irAEs.[19] Although this cohort included only four MPM patients in total 260 cases, none of them developed irAEs, therefore, it was still

unclear whether there is a correlation between irAEs and therapeutic effect in patients with MPM. In this study, we examined the eight patients with MPM, and showed the PFS in the patients with irAEs was significantly longer than their counterpart. To our best knowledge, it is a first report identifying the clinical factor which correlates the clinical benefits of ICIs treatment in patients with MPM.

In a phase II study (MERIT study), the treatments of ICIs in 4 out of 34 patients (12%) had to be terminated due to the adverse events.[7] In the present study, the treatments of nivolumab in two patients with pneumonitis and one patient with hypophysitis were discontinued and not rechallenged. On the other hand, there is another report that rechallenge of ICI was found to be effective in 7.4% of patients with various types of cancer, and 28.8% of these patients developed the same irAEs that occurred in the first treatment.[20] These results also support our findings that the ICIs have a potential to show the favorable clinical response in the patients with irAEs, therefore, to prevent the treatment from discontinuing or rechallenge it by careful monitoring and appropriate intervention would improve the outcome in these patients.

Our study has several limitations. Because MPM is a rare disease and nivolumab was approved for patients with MPM in 2018, sample size is small. It was a retrospective study and conducted in a single institution, so it may contain the selection bias. All histological types were epithelial type, so the correlation between irAEs and therapeutic effects in the other histological types remains unclear.

Conclusions

This is the first study to report the correlation between irAEs and therapeutic effect of nivolmab in patients with MPM. Because the presence of irAEs is associated with a favorable PFS, early detection and appropriate management of irAEs would enable us to treat these patients without discontinuation, resulted in improving the therapeutic benefits of this treatment.

Abbreviations

MPM: Malignant pleural mesothelioma

irAEs: Immune-related adverse events

PFS: Progression-free survival

OS: Overall survival

PD-1: Programmed cell death protein 1

ECOG: Eastern cooperative oncology group

PS: Performance status

NCI-CTCAE: National cancer institute-common toxicity criteria for adverse events

CR: Complete response

PR: Partial response

SD: Stable disease

PD: Progressive disease

RECIST: Response evaluation criteria in solid tumors

ORR: Overall response rate

DCR: Disease control rate

PD-L1: Programmed death-ligand 1

MSI-H: Microsatellite instability-high

ICIs: Immune checkpoint inhibitors

Declarations

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

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Contributions

HY: study design, data collection and analysis and interpretation, paper writing; HN and AM: study design, paper editing; RO, YY, HO and KO: data collection, paper editing; YN: study design and supervision.

Ethics declarations

Ethics approval and consent to participate

This single-center study was approved by Ethics Committee of Tokushima University. Because of its retrospective nature, the need for written informed consent was waived by the Ethics Committee of Tokushima University. All methods were carried out in accordance with Declaration of Helsinki.

Consent to publish

Not applicable.

Competing interests

Department of Respiratory Medicine and Rheumatology of Tokushima University has received research grant funding from Ono Pharmaceutical. HY, HN and KO have received speaker fees as honoraria from Ono Pharmaceutical. YN has received speaker fees as honoraria and Scholarship donation from Ono Pharmaceutical. The remaining authors declare that they have no conflicts of interest relevant to the subject of this manuscript.

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Figures

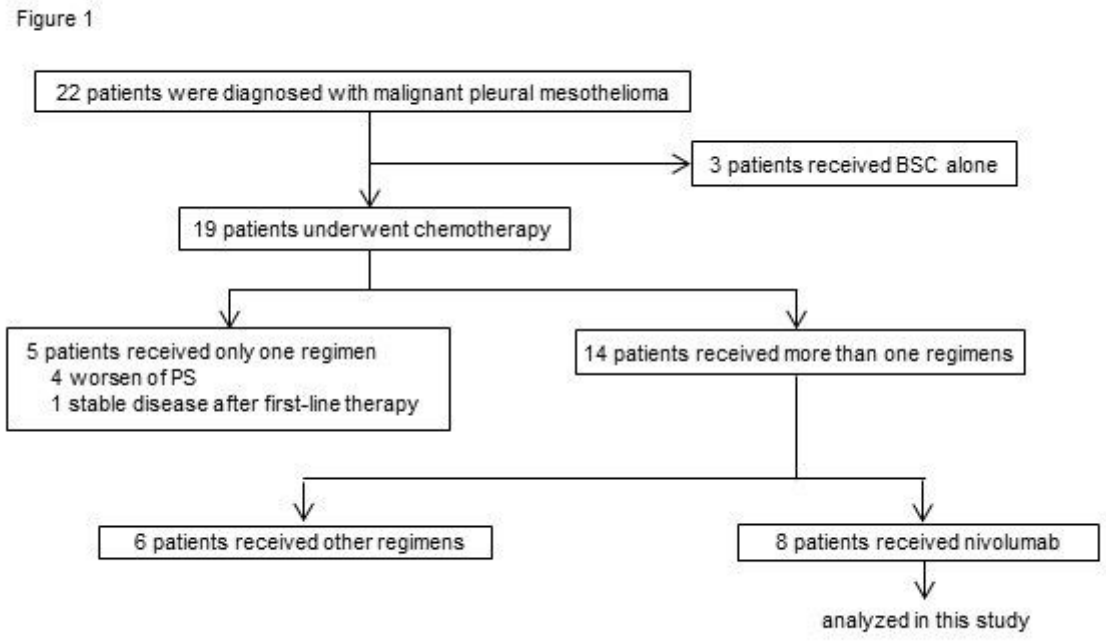

Figure 1

Flow diagram for study participants Abbreviations: BSC, best supportive care; PS, performance status; PD, progressive disease.

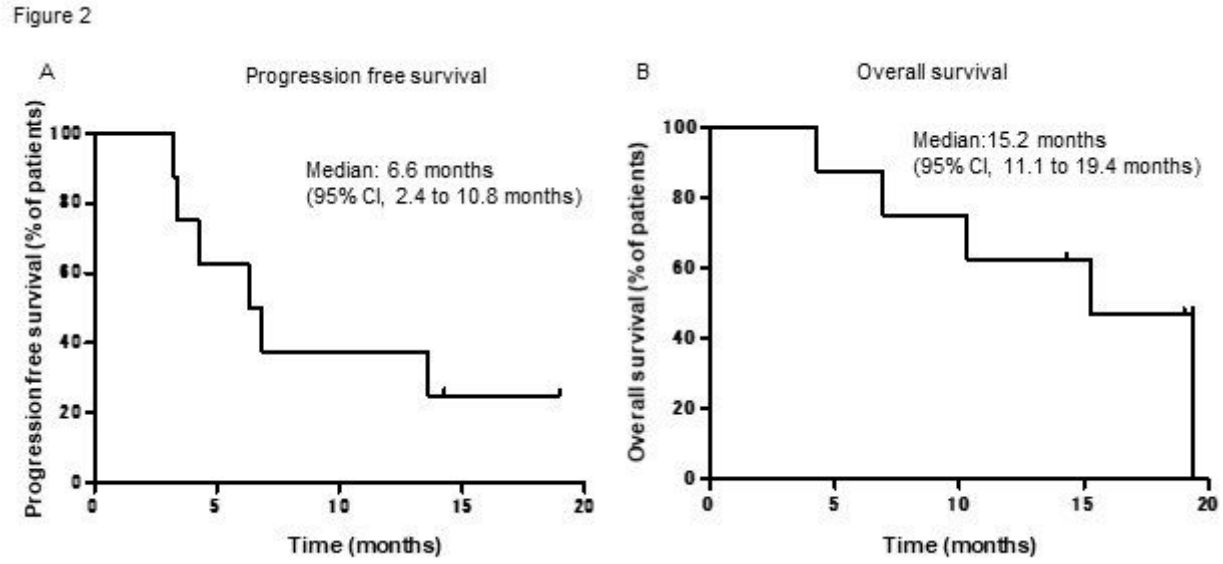

Figure 2

Kaplan-Meier survival curve of progression free survival (A) and overall survival (B) in previously treated MPM patients

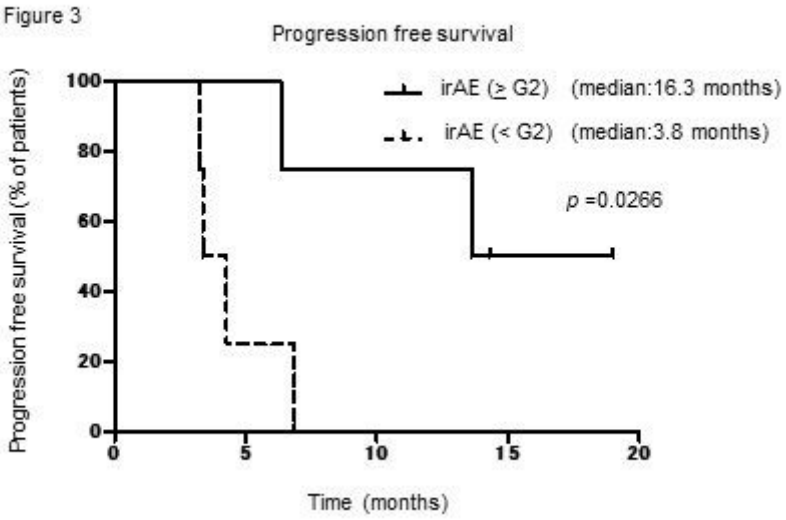

Figure 3

Correlation between irAEs and therapeutic effects Kaplan-Meier survival curve of PFS. PFS following nivolumab treatment in the grade 2 ≤ irAEs group (n = 4) and grade 2 > irAEs group (n = 4). The median PFS was significantly longer in the grade 2 ≤ irAEs group than in the grade 2 > irAEs group (p = 0.0266).