Department of Pharmacy[1], Komaki City Hospital; Department of Pharmacy[2], Ogaki Municipal Hospital; Laboratory of Drug Informatics[3], Gifu Pharmaceutical University, Gifu, Japan

Association between immune-related dermatologic adverse events and efficacy of pembrolizumab in non-small cell lung cancer patients

T. Fukuoka[1,*], Y. Yamamoto[1], J. Utsunomiya[1], E. Usami[2], M. Kimura[2], T. Yoshimura[2], M. Nakamura[3], Y. Toda[1]

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**Corresponding author: Tomohiro Fukuoka, Department of Pharmacy, Komaki City Hospital, 1-20 Jyobushi, Komaki-shi, Aichi 485-8520, Japan*
t.fukuoka.komakihp@gmail.com

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We retrospectively evaluated the incidence of skin immune-related adverse effects (irAEs) in patients treated with pembrolizumab (PMB) and explored and the relationship between skin irAEs and PMB efficacy. Thirty-two patients with non-small cell lung cancer treated with PMB between April 2017 and May 2018 were enrolled. The patients were separated into two groups, namely, skin irAEs and no-skin irAEs group. We investigated the ratio and degree of express skin irAEs, period of skin irAEs and treatment, and the PFS between the two groups. Additionally, we evaluated the PFS between the irAE and no-irAEs groups. The median patient age was 76.5 (range 56–92) years. The European Cooperative Oncology Group Performance Status (ECOG PS) score of 26, 5, and 1 was 0–1, 2, and 3, respectively. The male/female ratio was 23/9. In terms of clinical stages, 6, 21, and 5 patients were in stages III and IV, and postoperative relapse, respectively. Skin irAEs were observed in 10 patients (31%). The progression-free survival of patients with skin irAEs (median, 390 days) was longer than that of patients without skin irAEs (median, 128.5 days). Overall, we suggested a significant association between skin irAEs and the efficacy of PMB in treating non-small cell lung cancer. As skin irAEs can be an indicator of treatment efficacy, it is important for medical staff, including pharmacists, to closely observe these adverse events.

1. Introduction

Immune checkpoint inhibitors (ICIs), including pembrolizumab (PMB), with mechanisms different from those of cytotoxic anticancer drugs and molecular targeted drugs, are important therapeutic agents for various carcinomas, including non-small cell lung cancer (NSCLC). Pembrolizumab is a humanized monoclonal antibody that prevents the binding of PD-1 to its ligands, PD-L1 and PD-L2. Clinical trials have reported that PMB-based treatments improve progression-free survival (PFS) and overall survival of patients (Herbst et al. 2016; Reck et al. 2016). Pembrolizumab-based treatment for PD-L1 expression-positive NSCLC is widely used for both primary and subsequent treatments. However, ICIs are known to cause various immune-related adverse events (irAEs) in the body, including skin problems, thyroid dysfunction, diarrhea/colitis, and interstitial pneumonia. The incidence of adverse events caused by PMB is approximately 70%, including dermatologic irAEs (skin irAEs), fatigue, nausea, and reduced appetite. It has been reported that the incidence of skin irAEs such as rash and pruritus is 5%–15%, with grades 1 and 2 being more frequent (Ribas et al. 2015; Wang et al. 2017). The Clinical Practice Guidelines of the European Society for Medical Oncology recommends external steroids and oral antihistamines for grade 1 and 2 skin irAEs (Haanen et al. 2017).

Some studies have suggested that a correlation between the occurrence of irAEs and the efficacy of nivolumab in patients with NSCLC (Hasan et al. 2016; Teraoka et al. 2017; Sato et al. 2018). On the contrary, one study suggested that no correlation between the occurrence of irAEs and the efficacy of nivolumab in patients with malignant melanoma (Freeman-Keller et al. 2016). Patients treated with PMB often experience skin irAEs in clinical practice. However, skin irAEs such as rash and pruritus have not been investigated so far. Moreover, no study has evaluated the relationship between the occurrence of skin irAEs and the efficacy of PMB. We retrospectively investigated the incidence of skin irAEs in these patients and explored and the relationship between skin irAEs and the efficacy of PMB.

2. Investigations and results

2.1. Patient characteristics

Thirty-two patients with NSCLC were treated with PMB. Table 1 shows the patient's characteristics. There were no significant differences between the irAEs and no-skin irAEs groups in terms of age, sex, The European Cooperative Oncology Group Performance Status (ECOG PS), clinical stage, the tumor proportion score (TPS), and prior systemic therapy. The median patient age was 76.5 (range 56–92) years. The European Cooperative Oncology Group Performance Status (ECOG PS) scores of 26, 5, and 1 patients were 0–1, 2, and 3, respectively. The male/female ratio was 23/9. Regarding clinical stages, 6, 21, and 5 patients were in stages III and IV, and postoperative relapse, respectively. The number of patients with TPS of ≥50% was 25. The median number of patients with prior systemic therapy was 2 (range 1–5) (Table 1).

Table 1 Patient characteristics

	skin irAEs group (n = 10)	no-skin irAEs group (n = 22)	*P-value*
Age, years (median (min-max))	77 (63–82)	76 (56–92)	0.745[a]
Gender, n (%)			0.685[b]
Male	7 (70)	16 (73)	
Female	3 (30)	6 (27)	
ECOG PS*, n (%)			0.648[b]

	skin irAEs group (n = 10)	no-skin irAEs group (n = 22)	*P-value*
0-1	9 (90)	17 (77)	
≥ 2	1 (10)	5 (23)	
Clinical Stage, n (%)			0.865[b]
III	2 (20)	4 (18)	
IV	6 (60)	15 (68)	
Postoperative relapse	2 (20)	3 (14)	
TPS[†], n (%)			0.640[b]
≥ 50%	9 (90)	16 (74)	
< 50%	1 (10)	6 (26)	
Prior systemic therapy (median (min-max))	2 (1–5)	2 (1–4)	1.000[a]

* European cooperative oncology group performance status: ECOG PS
[†] Tumor Proportion Score: TPS
[a] Mann-Whitney U test
[b] Fisher s exact test

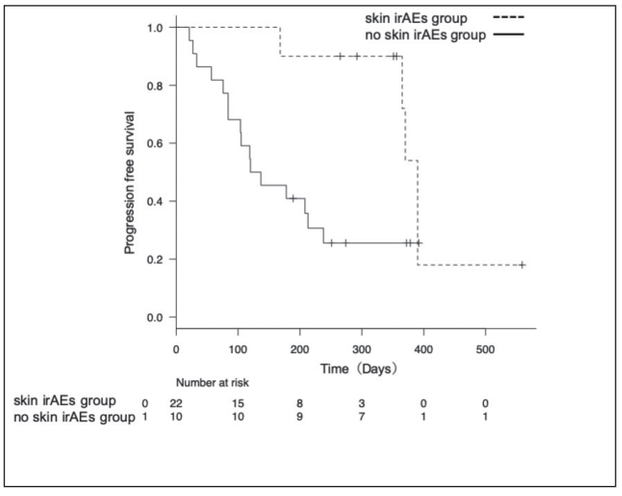

Fig. 1: Kaplan-Meier curve of progression free survival in patients with or without skin irAE

2.2. Ratio and degree of skin irAEs, and the time to skin irAE onset

Skin irAEs were observed in 10 of the 32 patients (31%). The median time to the onset of skin irAEs were 4.5 (range 2–10) cycles. The main skin irAEs were pruritus and rash. The number of patients with grade 1 and 2 irAEs was 5 each. There were no serious cases of ≥ grade 3 irAEs. External steroids and the anti-histamines were administered to patients with skin irAEs, and none of the patients received oral or intravenous steroids (Table 2).

Table 2: Time to onset skin irAEs and treatment

No.	The time to onset skin irAEs (cycle)	Grade	Treatment		
			The external steroid	the anti-histamines (topical)	the anti-histamines (systemic)
1	6	1	○	—	—
2	2	2	—	○	—
3	2	1	—	—	—
4	2	2	○	—	—
5	4	1	○	—	○
6	10	2	○	—	—
7	5	2	○	—	—
8	7	1	○	—	—
9	8	2	○	○	—
10	4	1	○	—	—

2.3. Progression free survival (PFS) of patients in the skin irAE and no-skin irAE groups

The PFS of patients with skin irAEs (median, 390 days [95% confidence interval (CI): 168 days to not reached]) was longer than that of patients without skin irAEs (median, 128.5 days [95% CI: 84–238 days], $P < 0.05$) (Fig. 1). Even after the occurrence of skin irAEs, PMB was continued. Three of the 10 patients with skin irAEs were continuing treatment at the time of analysis. One patient terminated the treatment due to the occurrence of irAEs different from skin irAEs, but the tumor had not progressed (Fig. 2).

2.4. Progression free survival (PFS) of patients in the irAE and no- irAEs groups

The PFS of patients with irAEs (median, 390 days [95% CI: 168 days to not reached]) was longer than that of patients without irAEs (median, 120 days [95% CI: 57–208 days], $P < 0.05$) (Fig. 3). The irAEs other than skin irAEs were endocrine disorders (n = 4), lung disorders (n = 3), and neurological disorders (n = 1). Furthermore, tumor progression was not observed in any of the patients regardless of the continuation or discontinuation of PMB due to the occurrence of irAEs other than skin irAEs (Fig. 4).

3. Discussion

In the present study, the PFS of patients with skin irAEs was longer than that of patients without skin irAEs. This suggests a significant association between skin irAEs and PMB efficacy in the treatment of NSCLC. In addition, the PFS of patients with irAEs was significantly prolonged compared with that of patients without irAEs. This indicates a relationship between the occurrence of irAEs and the efficacy of PMB.

Patients receiving PMB often experience only pruritus, without a rash. Wang et al. (2017) and Luo et al. (2018) reported that the incidence of pruritus increased in the ICI-treated group compared with that in the chemotherapy group. Thus, pruritus is considered an irAE caused by ICIs. In the present study, we focused on skin irAEs, including pruritus, and investigated the incidence of skin irAEs. A previous study reported that skin irAEs such as rash and pruritus were often observed in patients treated with PMB (Ribas et al. 2015; Wang et al. 2017; Sato et al. 2018). Similar to the findings of the previous study, skin irAEs were frequently observed in 35% of the patients in this study. Most of the skin irAEs were grade 2 or lower. None of the severe cases required oral or intravenous steroids using the external steroids or the anti-histamines.

On the basis of the findings, we suggest a significant association between skin irAEs and PMB efficacy in the treatment of NSCLC. Skin irAEs, especially pruritus, are often overlooked adverse events. As skin irAEs can be an indicator of treatment efficacy, it is important for medical staff, including pharmacists, to closely observe these adverse events. For early detection of skin problems, medical staff interview the patients and record their skin problems, including pruritus, in our hospital. As PMB can be continued even after the occurrence of skin irAEs, it is necessary to manage skin irAEs for a long time. Teraoka et al. (2017) reported that the PFS was prolonged in the rush group within 2 weeks and within 6 weeks after nivolumab administration. However, in this study, the PFS of patients was prolonged even when skin irAEs occurred after six weeks. This suggests that the PFS of patients could be prolomged even if skin irAEs occur regardless of the onset time. As reported by Sato et al. (2018), the PFS of patients with irAEs was significantly longer than that of patients without irAEs. Here, the administration of PMB was discontinued due to thyroid dysfunction and lung disorders. As there were cases in which the tumor did not progress despite the discontinuation of PMB, we considered that the effects of PMB were sustained even after the discontinuation of treatment. This is consistent with the findings of Sato et al. (2018) in patients with NSCLC administered nivolumab. However, it is not known exactly how long the efficacy of PMB lasts after its discontinuation

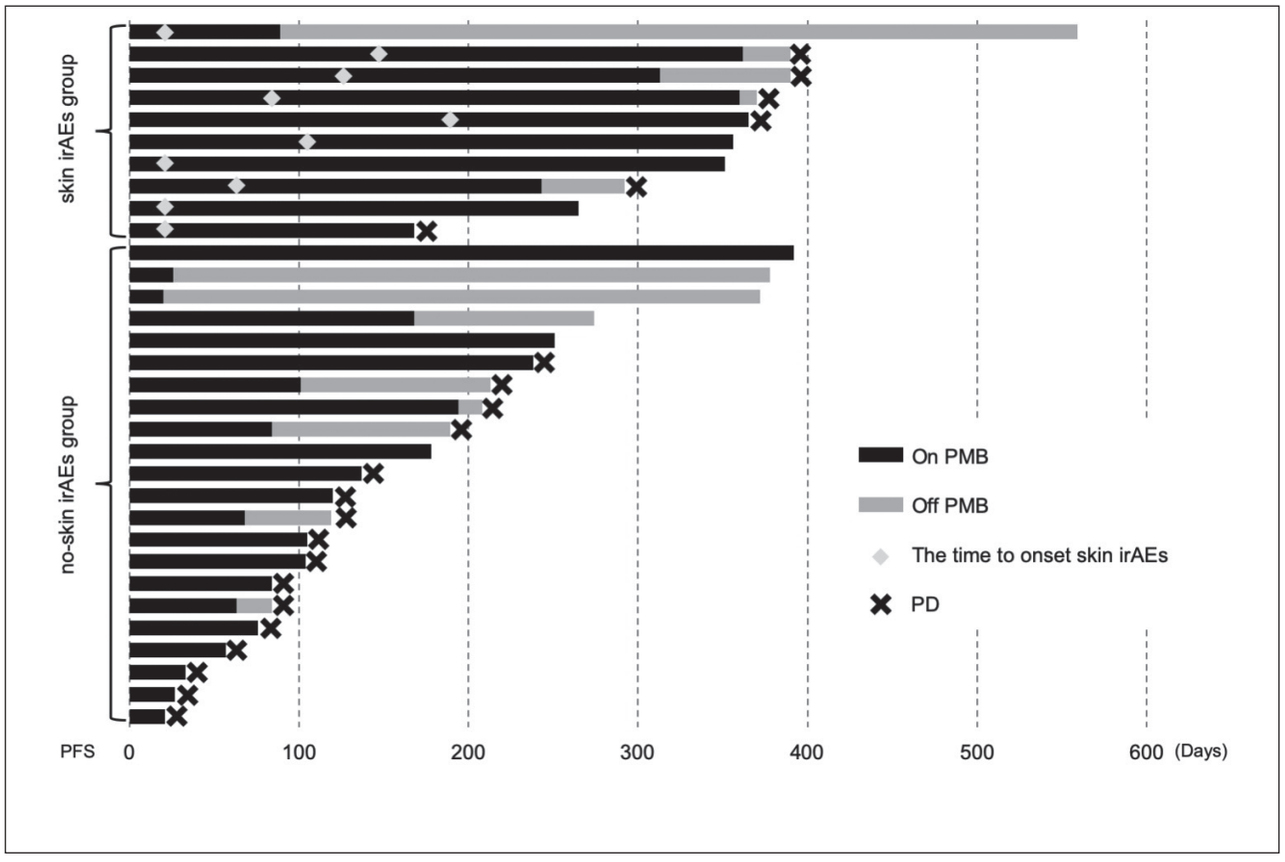

Fig. 2: Swimmer's plot of progression free survival in patients with or without skin irAE

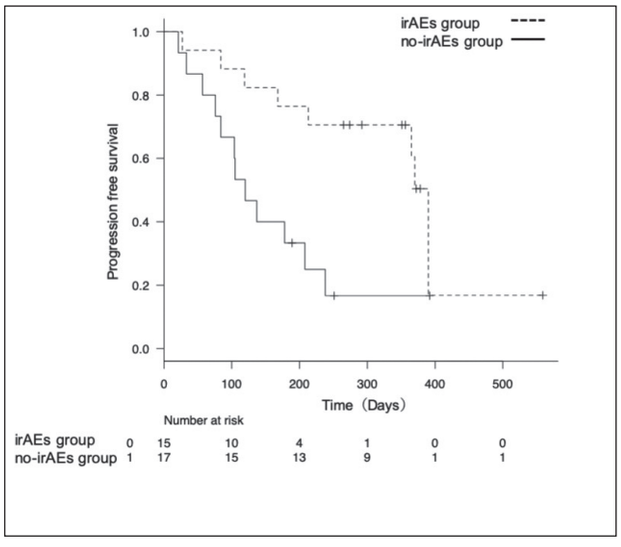

Fig. 3: Kaplan-Meier curve of progression free survival in patients with or without irAE

and whether the efficacy of PMB varies depending on the type of irAEs. Therefore, it is considered important to continue treatment while controlling irAEs. In this study, none of the patients discontinued treatment due to skin irAEs. Patients with the skin irAEs skin can continue treatment, and it is important to control the adverse events with external steroids and anti-histamines.

Our study had some limitations. This study was a single-center study, and the number of patients was low. As the data pertaining to skin irAEs were extracted from the medical records, it may not have been possible to extract all cases of pruritus. In addition, it cannot be denied that the cause of pruritus may be senile sebum deficiency; furthermore, it may include skin problems other than irAEs. Because it is difficult to distinguish the adverse events, it is necessary to consider the possibility of skin irAEs to continue treatment. Moreover, medical staff, including pharmacists, should know the medical history of patients to predict skin problems that occur after PMB administration. In conclusion, our findings suggest a significant association between skin irAEs and PMB efficacy in treating NSCLC. As skin irAEs can be an indicator of treatment efficacy, it is important for medical staff, including pharmacists, to closely observe these adverse events. Further multicenter and prospective studies are needed in this regard.

4. Experimental

4.1. Patient characteristics

Thirty-two patients with NSCLC treated with PMBat Komaki City Hospital (Komaki, Japan) between April 2017 and May 2018. Pembrolizumab (200 mg/body, every 3 weeks) was administered for 30 min via intravenous infusion. The following data of patients were gathered: age, sex, ECOG PS score, clinical stage, TPS, and prior systemic therapy.

4.2. Correlation between skin irAEs and PMB efficacy

The patients were separated into two groups, namely, skin irAEs and no-skin irAEs group. We investigated the ratio and degree of express skin irAEs, period of skin irAEs and treatment, and the PFS between the two groups. Additionally, we evaluated the PFS between the irAE and no-irAEs groups. The data cutoff date was October 31, 2018. Adverse events that may be caused by immunological mechanisms, such as thyroid dysfunction, skin problems, lung disorders, and neuropathies reported in previous studies (Naidoo et al. 2015; Luo et al. 2018) were defined as irAEs, and in this study, we also included pruritus as a skin irAE. Skin irAEs were evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) ver. 4.0, based on the medical record.

4.3. Statistical analysis

Mann–Whitney U test and Fisher's exact probability test were performed to compare the skin irAE and no-skin irAE groups. A log-rank test was performed to compare

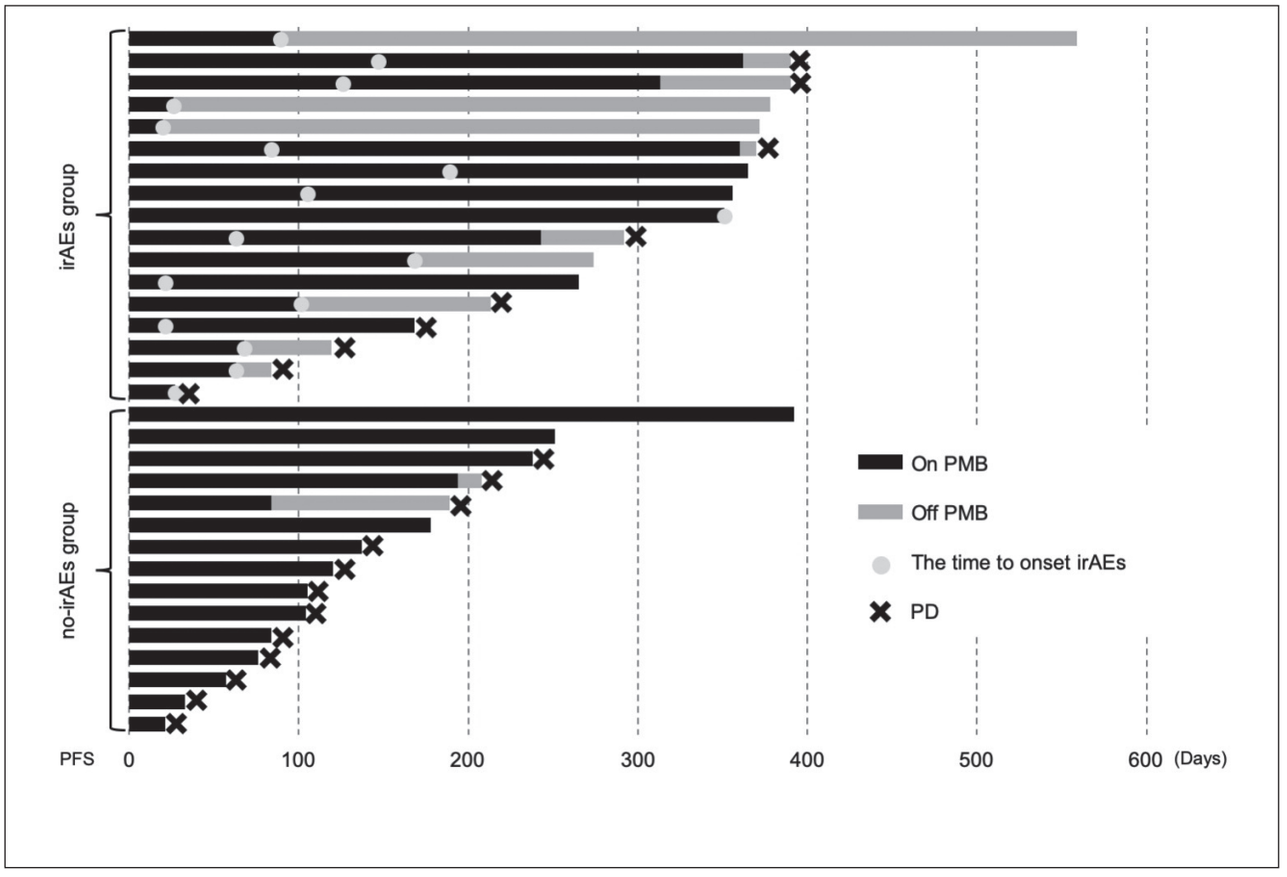

Fig. 4: Swimmer's plot of progression free survival in patients with or without skin irAE

the two groups. All statistical analyses were performed using EZR ver. 1.27 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R version 3.12 (R Foundation for Statistical Computing). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics (Kanda 2013). The *P*-values were two-sided, and $P < 0.05$ was considered to indicate a statistically significant difference.

4.4. Ethical considerations

This study was approved by the Institutional Review Board of the Komaki City Hospital (181038).

Conflict of interest: None declared.

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