Association Between Immune-Related Adverse Events and Clinical Efficacy in Patients with Melanoma Treated With Nivolumab: A Multicenter Retrospective Study

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ABSTRACT

Purpose: Nivolumab, an anti−programmed death 1 antibody, produces antitumor effects by activating host immunity, which also causes immune-related adverse events (irAEs). The aim of this study was to analyze the association between antitumor effect and irAEs induced by nivolumab in patients with melanoma.

Methods: Fifteen patients with melanoma who had received nivolumab at Tokushima University Hospital or Ehime University Hospital between January 2015 and December 2016 were enrolled in this study. Patients who had and did not have irAEs during nivolumab treatment were classified into an irAEs-positive group ($n = 8$) and an irAEs-negative group ($n = 7$), respectively. We compared the disease control rate (DCR) and overall survival (OS) between the 2 groups. Data on blood cell counts were also analyzed.

Findings: After a median of 4 cycles of nivolumab treatment, irAEs occurred. The DCRs were 75% and 14% in the irAEs-positive and irAEs-negative groups, respectively ($p < 0.05$). OS in the irAEs-positive group was higher than that in the irAEs-negative group ($p < 0.05$). Multivariable Cox proportional hazards regression analysis revealed that irAE occurrence affected OS with nivolumab treatment. Moreover, the increase in baseline peripheral lymphocyte count at the time of onset of irAEs was significantly greater in the irAEs-positive group than in the irAEs-negative group after 4 cycles of nivolumab treatment ($p < 0.05$).

Implications: Our study indicated that clinical response with nivolumab treatment improves with irAE occurrence in patients with melanoma. Moreover, the early increase in peripheral lymphocyte count may act as a biomarker for predicting the occurrence of irAEs induced by nivolumab. (*Clin Ther*. 2019;41:59−67)

Keywords: Biomarker, Immune-related adverse event, Melanoma, Nivolumab, Overall response rate.

Accepted for publication November 7, 2018
https://doi.org/10.1016/j.clinthera.2018.11.004
0149-2918/$ - see front matter

INTRODUCTION

Nivolumab is an immune checkpoint inhibitor that suppresses the interaction between programmed death (PD)-1 and its ligands (PD-L1 and PD-L2).[1] The interaction between PD-1 and its ligands inhibits the activation of T cells. The ligand of PD-1 is also expressed on the surface of cancer cells and inhibits the activation of tumor-specific T cells.[1] Tumor-specific T-cell activation induced by nivolumab inhibits various cancers with good clinical response rates.[2,3] It has been reported that cancers that have a high tumor mutation burden are more responsive to nivolumab treatment.[4] Because melanoma has a high frequency of tumor mutation burden, nivolumab is widely used for its treatment.[5] However, among patients with melanoma, some cases have poor response to nivolumab treatment. Therefore, identification of biomarkers to determine the therapeutic effect of nivolumab treatment in the early phase is urgent.

Activation of host immunity by nivolumab causes immune-related adverse events (irAEs) that affect various organs, such as the skin, endocrine systems, gastrointestinal tract, lungs, and liver.[6] Although activation of host immunity is beneficial for the antitumor effect of nivolumab, adequate management of irAEs is essential because irAEs are observed in the early phase of nivolumab treatment.[7,8] Previous studies have reported the association between the occurrence of irAEs and clinical response to nivolumab treatment in patients with non−small cell lung cancer.[9,10] These findings have indicated the possibility of occurrence of irAEs as an effective biomarker to determine the clinical response of nivolumab treatment in the early phase. In patients with melanoma, the association between nivolumab-induced vitiligo and good clinical response was reported.[11−13] Because vitiligo is one of the irAEs induced by the activation of host immunity, we hypothesized that there is an association between the occurrence of irAEs after nivolumab administration and clinical response. Therefore, this multicenter retrospective study was conducted to analyze the association between antitumor effect and irAEs induced by nivolumab in patients with melanoma.

Patients and Methods Study Design

Patients who had received a first administration of nivolumab at Tokushima University Hospital or Ehime University Hospital between January 2015 and December 2016 were enrolled in this study. Patients were excluded if they had stopped nivolumab treatment within 3 cycles or if they had preexisting autoimmune comorbidities. Fifteen patients were eligible for this study. Nivolumab was administered intravenously at 2 mg/kg every 3 weeks or 3 mg/kg every 2 weeks according to the dosing method established by the National Health Insurance System of Japan. These patients were classified into irAEs-positive ($n = 8$) and irAEs-negative ($n = 7$) groups. The details of patient selection are shown in Figure 1. Nivolumab-induced irAEs included rash, endocrine dysfunction, gastrointestinal symptoms, liver dysfunction, renal dysfunction, thrombocytopenia, peripheral neuropathy, and interstitial pneumonia with reference to past studies.[14−16] They were graded according to the Common Terminology Criteria for Adverse Events, version 4.0, commonly used for evaluation of adverse events in chemotherapy. We collected the following patient data: age, sex, weight, stage of melanoma, treatment courses before the initiation of nivolumab treatment, course of nivolumab treatment, total dose of nivolumab, *BRAF* mutation status, and laboratory data before nivolumab treatment. Creatinine clearance was calculated as described by Cockcroft and Gault.[17] Patients continued nivolumab treatment until they were evaluated as having progressive disease, died, experienced unacceptable AEs, or offered to stop the treatment. Patients who stopped nivolumab treatment continued to be observed until death or until they were lost to follow-up (median follow-up duration, 470 days). This study was performed in accordance with Japanese governmental ethical guidelines. The survey content and methods to protect personal information were approved by the Tokushima University Hospital Ethics Committee and Ehime University Hospital Ethics Committee and were in accordance with the stipulations on the handling of patient personal information (Ethics Committee Registration No. 2508-3). Japanese law does not require individual informed consent from participants in a noninvasive observational trial, such as the present study. We therefore used our official website as an opt-out method rather than acquiring written or oral informed consent.

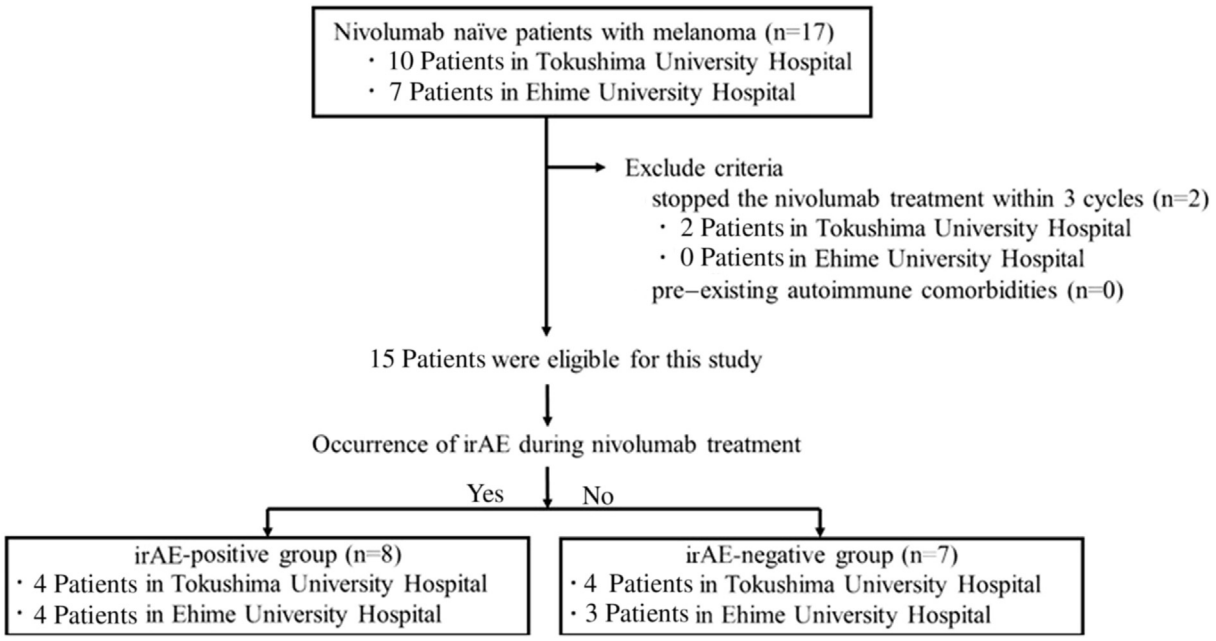

Figure 1. Study design. Nivolumab-induced immune-related adverse events (irAEs) included rash, endocrine dysfunction, gastrointestinal symptoms, liver dysfunction, renal dysfunction, thrombocytopenia, peripheral neuropathy, and interstitial pneumonia.

Evaluation of DCR and OS

Clinical response to nivolumab treatment was evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. Disease control rate (DCR) was defined in terms of complete response, partial response, or stable disease at the first evaluation of clinical response by computed tomography. Overall survival (OS) was defined based on the period from the date on which patients started nivolumab treatment until the date of death or last follow-up.

Evaluation of Peripheral Blood Cell Counts

Baseline blood cell counts were defined as the counts determined within 21 days before initiating nivolumab treatment. Relative increase in each blood cell count or neutrophil-to-lymphocyte ratio (NLR) in the irAEs-positive group was calculated as the ratio of the value at the time of onset of irAEs to the baseline value. Relative increase in each blood cell count or NLR in the irAEs-negative group was calculated as the ratio of the value after 4 cycles of nivolumab treatment to the baseline value.

Statistical Analysis

The clinical laboratory values were not normally distributed; therefore, the Mann−Whitney *U* test was used to analyze proportional scales. The Fisher exact test was used to analyze the nominal scales. The OS was compared by using the Kaplan−Meier plot and log rank test. Multiple Cox proportional hazards regression analysis was conducted using factors selected by stepwise methods after determining variables with $p < 0.1$ on comparing the 2 groups. All recorded p values were 2-sided, and differences with $p < 0.05$ were considered significant. All analyses were performed using JMP software, version 11 (SAS Institute Japan Ltd, Tokyo, Japan).

RESULTS

Patient Characteristics and irAE Profile

Table I gives the characteristics of patients in the irAEs-positive and irAEs-negative groups. Age, sex, treatment courses before the initiation of nivolumab treatment, course of nivolumab treatment, and total dose of nivolumab were not different between the 2

Table I. Patient characteristics.

Characteristic	irAEs-Negative Patients ($n = 7$)	irAEs-Positive Patients ($n = 8$)	p
Males/females	1/6	3/5	0.57*
Melanoma grading stage ¾	0/7	1/7	1.00*
Age, median (range), y	53 (25–78)	70.5 (38–89)	0.06†
BRAF mutation, yes/no/unknown	1/6/0	1/5/2	0.36*
No. of posttreatment courses, median (range)	1 (0–2)	1(0–4)	0.90†
No. of courses of nivolumab treatment, median (range)	7 (4–19)	11 (7–18)	0.35†
Total dose of nivolumab, median (range), mg	1170 (354–2279)	1357 (529–2340)	0.54†
Laboratory data before nivolumab treatment, median (range)			
White blood cells,/μL	6000 (3800–8800)	4600 (2900–10100)	0.29†
Neutrophil,/μL	4420 (2110–5420)	2900 (1440–3630)	0.04†
Lymphocyte,/μL	1610 (790–2720)	1070 (540–1650)	0.28†
Neutrophil-to-lymphocyte ratio	2.76 (1.99–3.64)	2.57 (1.44–4.74)	0.61†
Aspartate aminotransferase, IU/L	17 (14–41)	23 (15–47)	0.18†
Alanine aminotransferase, IU/L	13 (10–51)	22 (7–38)	0.45†
Creatinine clearance, mL/min	85 (12–160)	66 (25–79)	0.40†
Duration for the first evaluation of nivolumab treatment, median (range), d	75 (33–128)	113 (40–231)	0.07†

irAEs = immune-related adverse events.
* Fisher exact test.
† Mann–Whitney *U* test.

groups. Positive *BRAF* mutation results were observed in 1 patient in each group, and 6 patients in the irAEs-positive group and 5 in the irAEs-negative group had negative *BRAF* mutation results. The *BRAF* mutation status in 2 patients in the irAEs-positive group was unknown. Baseline peripheral neutrophil count in the irAEs-positive group was lower than that in the irAEs-negative group. Other laboratory data were not different between the 2 groups. Moreover, the period from the start of nivolumab treatment to the first evaluation of clinical response did not differ.

The profile of irAEs observed in our study is given in Table II. Of the 8 patients who experienced irAEs, 5 patients experienced multiple irAEs. irAEs occurred after 4 cycles (median) of nivolumab administration. In our study, no patient experienced irAEs of higher than grade 3. Rash (40%), hypothyroidism (27%), diarrhea (13%), and liver dysfunction (7%) were observed, and no other irAEs were observed in our study.

Association of Occurrence of irAEs With Clinical Response After Nivolumab Treatment

In the irAEs-positive group, partial response and stable disease were observed in 2 and 4 patients, respectively. In the irAEs-negative group, stable disease was observed in 1 patient. DCRs were 75% and 14% in the irAEs-positive and irAEs-negative groups, respectively ($p < 0.05$) (Figure 2A). OS in the irAEs-positive group was higher than that in the irAEs-negative group ($p < 0.05$) (Figure 2B). Multivariable Cox proportional hazards regression analysis revealed that occurrence of irAEs affected OS on nivolumab treatment (Table III).

Analysis of Blood Cell Counts

The increase in baseline peripheral lymphocyte count was significantly greater in the irAEs-positive group than in the irAEs-negative group ($p < 0.05$) (Figure 3A). However, peripheral neutrophil count did not change from baseline in each group

Table II. Profile of immune-related adverse events.

Variable	No. (%) of patients or median (range) (n = 15)
Patients with irAEs	8 (53)
Patients with multiple irAEs	5 (33)
Median time of irAEs onset, No. of cycles of nivolumab treatment	4 (3–6)
Grade	
1	11 (85)
2	2 (15)
≥3	0 (0)
Type of irAEs	
Rash	6 (40)
Hypothyroidism	4 (27)
Diarrhea	2 (13)
Liver dysfunction	1 (7)

irAEs = immune-related adverse events.

Table III. Multivariable Cox proportional hazards regression analysis of the effect of irAE development on overall survival.

Parameter	Hazard ratio (95% CI)	p
Occurrence of irAEs	0.01 (<0.01–0.88)	0.045
Neutrophil count	0.25 (0.05–1.30)	0.10
Age	0.93 (0.86–1.01)	0.12

irAEs = immune-related adverse events.

(Figure 3B). NLR tended to decrease from baseline in the irAEs-positive group, but it was not significantly different between the 2 groups (Figure 3C).

DISCUSSION

Nivolumab, an immune checkpoint inhibitor, was first approved in Japan in 2014. It was first approved for melanoma treatment before all cancer types and produced better clinical response than existing treatments.[18] Treatment of patients with no *BRAF* mutation is limited because these patients cannot

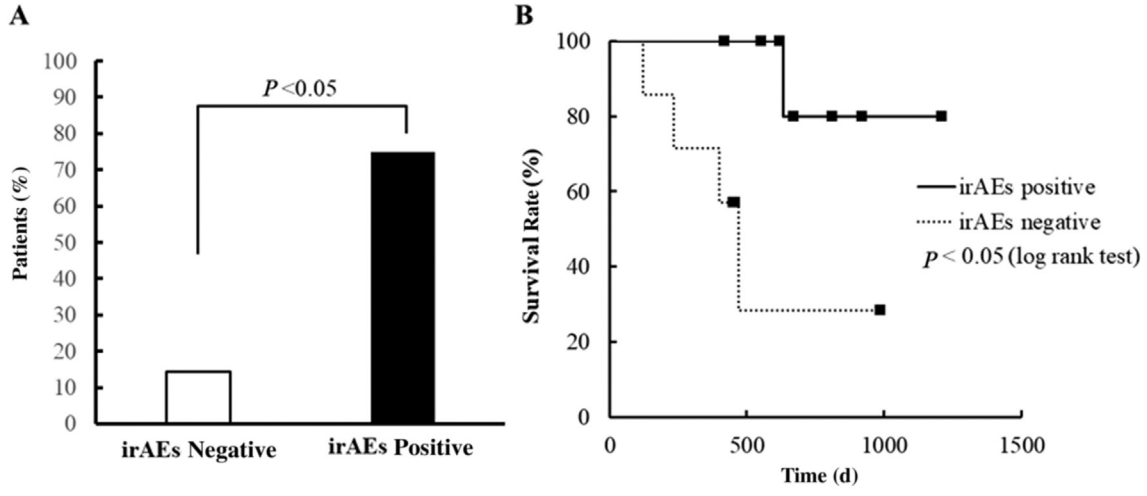

Figure 2. Association between immune-related adverse events (irAEs) and clinical response to nivolumab treatment. (A) Comparison of disease control rate (DCR) between patients with and without irAEs. DCR was performed based on Response Evaluation Criteria in Solid Tumors, version 1.1 at the first computed tomography after nivolumab treatment. (B) Kaplan–Meier plot comparing overall survival in patients with and without irAEs. Black squares indicate censored cases at last follow-up.

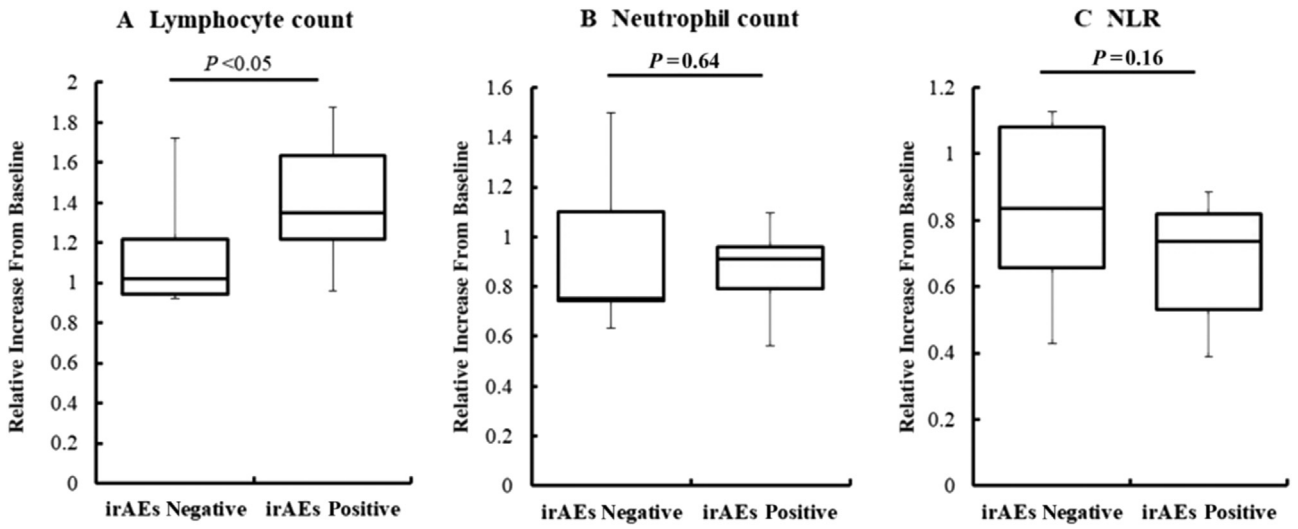

Figure 3. Comparison of blood cell counts between patients with or without immune-related adverse events (irAEs). Comparison of lymphocyte count (A), neutrophil count (B), and neutrophil-to-lymphocyte ratio (NLR) (C) between patients with and without irAEs. Relative increase in each cell count in the irAEs-positive group was calculated as the ratio of the value at the time of onset of irAEs and the baseline value. Relative increase in each cell count in the irAEs-negative group was calculated as the ratio of the value after 4 cycles of nivolumab treatment and the baseline value. N.S. = nonsignificant.

be treated using *BRAF* inhibitors.[19] Therefore, nivolumab is the key drug for melanoma treatment. However, previous studies have reported that there are nonresponders to nivolumab treatment.[18] Thus, a biomarker to determine clinical response during the early phase of nivolumab treatment is necessary. Despite its antitumor effect being related to the activation of the host immune system, how the occurrence of irAEs affects the clinical response rate with nivolumab treatment is not clearly known. Freeman–Keller et al[11] revealed that OS was longer in patients with melanoma who had rash induced by nivolumab than in patients who did not experience this AE. However, most patients in this study were concomitantly administered cancer-specific peptides. Therefore, the association between occurrence of irAEs induced by nivolumab alone and clinical response remained unclear. Our multicenter retrospective study clarified the dichotomous association between irAEs induced by nivolumab in early phase and clinical efficacy in patients with melanoma. Previous reports on other solid tumors indicate that irAEs such as rash and endocrine dysfunction improve clinical response with nivolumab treatment.[9,10] Although more analyses in patients with other cancer types are necessary, this finding indicates that the association between occurrence of irAEs and better clinical response may be observed irrespective of cancer type. PD-1 and cytotoxic T-lymphocyte–associated antigen-4, termed the immune checkpoint molecule, have roles in self-tolerance. The inhibition of these molecules activates not only the tumor-specific T cells but also autoimmunity. Tumor-specific neoantigens and normal tissue antigens could be cross-reactive. These mechanisms may be related to the relation between the occurrence of irAEs induced by nivolumab and good clinical response. The difference in the profile of irAEs of different immune checkpoint inhibitors was reported. For example, the frequency of dermatologic adverse events induced by cytotoxic T-lymphocyte–associated antigen-4 inhibitors was higher than that induced by PD-1 inhibitors.[20] This finding indicates that it is necessary to analyze the association between the type of irAEs and clinical effect between different immune checkpoint

inhibitors. We then analyzed the association between onset of early-phase irAEs and clinical response to nivolumab because focusing on early-onset irAEs may be more useful than focusing on late-onset irAEs. In our study, irAEs induced by nivolumab were observed after a median of 4 cycles of nivolumab treatment. Our study indicated that the early onset of irAEs may be a biomarker for the clinical response, and the management of irAEs is important for nivolumab treatment. Corticosteroid is empirically administered to treat irAEs. However, early use of corticosteroid during nivolumab treatment is reported to decrease clinical benefit in patients with non–small cell lung cancer.[21] Therefore, we should carefully use corticosteroid for irAE treatment.

The increase in baseline peripheral lymphocyte count in the irAEs-positive group after nivolumab administration indicated that measurement of the peripheral lymphocyte count may help predict the occurrence of irAEs induced by nivolumab. Because some irAEs are less likely to appear as subjective symptoms, specific examinations are required to diagnose irAEs. Our study suggested that the combination of monitoring peripheral lymphocyte count and specific examination may be able to increase the sensitivity to diagnose irAEs. Moreover, because counting of peripheral lymphocytes is a routine test in cancer treatment, its clinical applicability is high. In our study, irAEs occurred with the increase in lymphocyte count, including rash, endocrine dysfunction, and diarrhea. These adverse events were the main irAEs caused by nivolumab. Therefore, monitoring peripheral lymphocyte count may be useful to predict the occurrence of irAEs. Previous studies have also found that increases in peripheral lymphocyte count after nivolumab treatment are associated with better clinical response in patients with lung cancer and melanoma.[22,23] The interaction of PD-1 with PD-L1 prevents the activation and proliferation of T cells. Inhibition of PD-L1 binding with PD-1 induces T-cell activation in the priming phase and increases the number of cytotoxic T cells.[24] Diehl et al[22] reported that lymphocytopenia affected progression-free revival in patients receiving immune checkpoint inhibitor, which may be related to antitumor T-cell dysfunction resulting from immune exhaustion and depletion. These results indicate that the increase in the number of peripheral lymphocytes may be related to enhancement in the antitumor effect and occurrence of irAEs induced by nivolumab.

Baseline NLR and changes in NLR during nivolumab treatment act as indicators of the antitumor effect of nivolumab in solid tumors.[25,26] Moreover, high NLR before nivolumab treatment is associated with poor clinical response.[27] In our study, although lymphocyte count was increased in the irAEs-positive group, no correlation was found between NLR and the occurrence of irAEs or antitumor effect of nivolumab. Therefore, further studies are needed to confirm the utility of determining changes in NLR to evaluate the clinical efficacy of nivolumab.

Our study has certain limitations. First, the sample size is small in our study, and there is a possibility that the statistical power for evaluating our results is not sufficient. Because an analysis with small sample size leads to type 2 error, further prospective analyses with more patients are needed to confirm our findings. Second, in our study, no patients had irAEs of higher than grade 3 severity; however, such irAEs were observed in 2% of the patients in a previous study.[6] We could not analyze the association between the severity and type of irAEs and clinical response because of the small sample size. For example, musculoskeletal adverse events, which are rarely reported in nivolumab-treated patients, were not observed in our study.[20] Analyzing these associations is beneficial to evaluating our findings. Third, pseudoprogression is related to good therapeutic response after disease progression in immune checkpoint inhibitor treatment.[28] Therefore, adhering to RECIST may not be sufficient to determine the therapeutic effect.[29] Because pseudoprogression was not observed in our study, we followed RECIST to judge the clinical response. Fourth, lymphocyte count varies with infection or concomitant medication. Although no patients received corticosteroids or immunosuppressants that could affect the blood cell counts after 4 cycles of nivolumab treatment, a thorough verification of the patient background at the time of blood cell counting should have been performed. Fifth, the expression of PD-L1 in tumors was not tested in our study. Because low expression of PD-L1 is reported to contribute to treatment failure, testing of PD-L1 expression is necessary. The relation between PD-L1 status and the occurrence of

irAEs is also unknown. Moreover, the follow-up time was not long enough to fully analyze long-term survival outcome. We could not analyze the effect of comorbid conditions on the development of irAEs because of the retrospective nature of the study and the small sample size. To overcome these limitations and increase the reliability of our results, we are currently planning a prospective study with more patients treated with PD-1 or PD-L1 inhibitors.

CONCLUSION

The findings of the present study indicate that occurrence of irAEs in the early phase improves clinical response to nivolumab treatment. Our study emphasizes that adequate management of irAEs is necessary to prevent overcompensation of clinical response. Peripheral lymphocyte count is useful to predict the occurrence of irAEs in the early phase. Although further prospective analyses with more patients are required to confirm these findings, considering the association of irAEs with clinical response to nivolumab treatment, the early detection of irAEs based on lymphocyte count monitoring and adequate management of irAEs would allow achieving the maximum clinical response with nivolumab treatment in patients with melanoma.

FUNDING SOURCES

This study was supported by grant 17K15506 from the Japan Society for the Promotion of Science Grants-in-Aid for Scientific Research.

CONFLICTS OF INTEREST

None declared.

ACKNOWLEDGMENTS

N. Okada performed the survey of electronic records, performed the statistical analyses, and drafted the manuscript. H. Kawazoe, Y. Matsudate, and R. Utsunomiya performed the survey of electronic records. K. Takechi and N. Hidaka facilitated data collection from the 2 centers. Y. Kubo, K. Sayama, A. Tanaka, and K. Ishizawa were involved in the design of the study and helped in drafting the manuscript. M. Goda, M. Imanishi, Y. Zamami, and M. Chuma assisted with study design. All authors approved the final manuscript.

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