Clinical and Translational Oncology (2020) 22:919–927
https://doi.org/10.1007/s12094-019-02214-8

RESEARCH ARTICLE

Safety and efficacy of PD-1/PD-L1 blockade in patients with preexisting antinuclear antibodies

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Received: 22 August 2019 / Accepted: 13 September 2019 / Published online: 1 October 2019

Abstract

Purpose Immune checkpoint inhibitors (ICIs) show promising clinical activity in advanced cancers. However, the safety and efficacy of PD-1/PD-L1 blockade in patients with preexisting antinuclear antibodies (ANA) are unclear.

Methods 191 patients treated with nivolumab, pembrolizumab, atezolizumab, or durvalumab for unresectable advanced cancers between September 2014 and December 2018 were identified retrospectively. Patients were divided into positive (ANA titers ≥ 1:160) and negative ANA groups (ANA titers < 1:160). Development of immune-related adverse events (irAEs), the overall response rate (ORR), and disease control rate (DCR) were monitored.

Results Positive ANA titers were seen in 9 out of 191 patients. Four patients in the positive ANA group and 69 patients in the negative group developed irAEs of any grade without a significant difference between the groups. The development of endocrine, pulmonary, and cutaneous irAEs was not significant, whereas positive ANA was significantly higher in patients who developed colitis (2/9) than in patients who did not (3/182, $P = 0.0002$). DCR in the positive and negative ANA group was 37.5% and 67.5%, respectively, and was not statistically significant, but had better efficacy in patients without ANA ($P = 0.08$). ANA-related autoimmune diseases such as SLE, Sjögren's syndrome, MCTD, scleroderma, dermatomyositis, and polymyositis was not induced in either group. However, one patient with preexisting dermatomyositis had a flare up after initiation of atezolizumab.

Conclusion Further studies to identify predictive factors for the development of irAEs are required to provide relevant patient care and maximize the therapeutic benefits of ICIs.

Keywords Immune-related adverse events · Programmed cell death 1 blockade · Immune checkpoint inhibitors · Antinuclear antibodies · Autoimmune diseases

Abbreviations

ICI	Immune checkpoint inhibitors
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death ligand 1
NSCLC	Non-small cell lung cancer
MM	Malignant melanoma
irAEs	Immune-related adverse events
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
ANA	Antinuclear antibodies
PFS	Progression-free survival
OS	Overall survival
ORR	Overall response rate
DCR	Disease control rate
PS	Performance status

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s12094-019-02214-8) contains supplementary material, which is available to authorized users.

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Introduction

Immune checkpoint inhibitors (ICIs), especially antibodies targeting the programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1), have improved outcomes for a variety of advanced cancers including non-small cell lung cancer (NSCLC), malignant melanoma (MM), renal cell carcinoma, urothelial cancer, head and neck cancer, gastric cancer, and Hodgkin's lymphoma [1–6]. The

ability of neoplastic cells to hide from the immune system is one of the hallmarks of cancer [7, 8] and the clinical success of immunotherapeutic strategy highlights the role of the immune system in controlling cancer progression.

Disruption of PD-1/PD-L1 pathway by monoclonal antibodies reactivate and enhance T-cell-mediated antitumor immunity, however, this may cause immune-related adverse events (irAEs), such as cutaneous disorders, thyroid dysfunction, endocrinopathies, pneumonitis, and colitis [9]. Occasionally, these events require systemic immunosuppression or discontinuation of treatment. Therefore, it is important to classify patients who have a high possibility of developing irAEs for relevant patient care and optimization of therapy.

Antinuclear antibodies (ANA), a heterogeneous group of autoantibodies against nuclear antigens is an invaluable tool for the primary care and subspecialty settings and offers a window of opportunity for further clinical investigation of suspected autoimmune diseases. It is also frequently used as a screening tool before induction of ICIs. Among healthy individuals, there is a certain percentage who are ANA positive. An earlier study of healthy individuals showed that 31.7% at 1:40, 13.3% at 1:80, 5.0% at 1:160, and 3.3% at 1:320 serum dilution were positive for ANA [10]. The percentage of positive ANA is even higher in elderly individuals and patients with malignancies [11]. There remains a widespread and explicit reluctance to use PD-1/PD-L1 antibodies in patients with preexisting positive ANA due to concerns of exacerbating the underlying autoimmune disorder and/or induction of severe irAEs. However, to our knowledge, only a few studies have assessed the correlation between the development of irAEs and preexisting ANA.

The aim of this study was to assess the safety and efficacy of PD-1/PD-L1 antibody treatment in patients with preexisting ANA.

Materials and methods

Patients

We performed a retrospective review of electronic medical records of 216 patients who received nivolumab, pembrolizumab, atezolizumab, or durvalumab as monotherapy for metastatic or unresectable advanced cancers from September 2014 to December 2018 at Kyoto Prefecture University of Medicine. Among these patients, 25 were excluded for the following reasons: no estimated ANA in 15 patients and the other 10 patients were administered PD-1/PD-L1 blockade only once. None of the patients had a history of pretreatment with other ICIs such as ipilimumab, which is an anti-cytotoxic T-lymphocyte associated protein 4 (CTLA-4) antibody. The treatment was provided until progression of disease or unacceptable toxicity was noted. All patients were followed up until death or loss of contact. This study was approved by the Medical Ethics Review Committee of the Kyoto Prefectural University of Medicine (Approval No. ERB-C-867-1). Given the retrospective nature of this work, informed consent was waived for the individual participants included in the study in accordance with the standards of the Kyoto Prefectural University of Medicine Institutional Medical Ethics Review Committee.

Assessments

All the patients received PD-1/PD-L1 blockade intravenously, according to a schedule of 3 mg/kg or 240 mg every 2 weeks for nivolumab, 2 mg/kg every 3 weeks for pembrolizumab, 1200 mg every 3 weeks for atezolizumab, and 10 mg/kg every 2 weeks for durvalumab. Patients were screened at the beginning of treatment for baseline serum ANA by an indirect immunofluorescence method. We used an ANA titer cutoff of $\geq$ 1:160 based on an earlier report which showed that an ANA cutoff at 1:160 serum dilution has high specificity with ability to exclude 95% of normal individuals [10]. However, the cutoff of ANA titers has not been fully established yet, and so we analyzed identically using a cutoff at ANA titers $\geq$ 1:80 and titers $\geq$ 1:40 for supplementary information.

The patients were divided into two groups: the positive ANA group (patients with ANA titers $\geq$ 1:160) and the negative ANA group (patients with ANA titers < 1:160). The development and severity of representative irAEs namely, thyroid dysfunction, cutaneous disorders, interstitial pneumonitis, colitis, hypophysitis, and diabetes were estimated. The severity of irAEs was graded according to the CTCAE 4.0 criteria. The patients' characteristics such as gender, age, performance status (PS), type of tumor, prior therapy lines, treatment cycles, and follow-up period were retrieved from medical records. PS was based on the Eastern Cooperative Oncology Group (ECOG) scale.

The overall response rate (ORR) and disease control rate (DCR) were evaluated in this study. ORR was defined as the proportion of patients who had a partial or complete response to therapy, whereas DCR was defined as the proportion of patients who had a partial or complete response to therapy or stable disease. Evaluation of clinical responses was based on the laboratory findings and the Response Evaluation Criteria in Solid Tumors (RECIST) version1.1. All patients were evaluated after the first 2–3 cycles and were followed by computed tomography (CT) scans or magnetic resonance imaging (MRI) every 2–3 months.

Statistical analysis

Continuous variables were presented as median with range according to their distribution. The Mann–Whitney *U* tests were used to compare continuous variables between the positive and negative ANA groups. The Chi-square test or Fisher's exact test was used to compare categorical variables between the two groups. All statistical tests were two-sided, and $P < 0.05$ was set as the level of significance. All statistical analyses were performed using JMP® 13 (SAS Institute Inc., Cary, NC, USA).

Results

Baseline characteristics

This study group of 191 patients consisted of 73 patients with non-small cell lung carcinoma (NSCLC), 33 with malignant melanoma (MM), 30 with head and neck cancer, 27 with renal cell carcinoma, 19 with gastric cancer, and 9 with urothelial cancer. Of these patients, 142 received nivolumab, 41 received pembrolizumab, 6 received atezolizumab, and 2 received durvalumab. At the time of analysis, the median follow-up duration was 31 weeks (range 2–224 weeks). The median number of treatment cycles was 7.5 (range 2–76). The baseline clinical characteristics of the patients in the positive and negative ANA groups are shown in Table 1. There were no significant differences in age, gender, performance status (PS), treatment cycles, follow-up period, tumor type, prior therapy lines, type of PD-1/PD-L1 blockade administered, and preexisting autoimmune disease among the two groups. Two patients with ANA titers under 1:160 were in use of corticosteroids or immunosuppressants for their autoimmune disease at baseline.

Development of irAEs

Positive ANA was observed in 9 of 191 patients (4.7%). Among the positive ANA group, three patients had 1:160, two patients had 1:320, three patients had 1:640, and one patient had 1:1280 (Fig. 1) serum dilution ratios, respectively. Table 2 shows in detail the development of irAEs among the two groups. Four patients in the positive ANA

Table 1 Baseline characteristics

	Positive ANA $N=9$	Negative ANA $N=182$	*P* value
Age (median)	68 (52–80)	70 (29–89)	0.28
Gender: male/female	5/4	124/58	0.43
PS			0.39
0	7	103	
1	1	59	
≤ 2	1	20	
Treatment cycles (median)	6 (3–17)	8 (2–76)	0.39
Follow-up period (week, median)	33 (6–89)	30 (2–224)	0.67
Tumor type			0.44
NSCLC	4	69	
MM	3	30	
Head and neck	0	30	
RCC	2	25	
Gastric	0	19	
Urothelial cancer	0	9	
Prior therapy lines ≤ 1/≤ 2	4/5	101/81	0.52
Treatment			0.84
Nivolumab	7	135	
Pembrolizumab	2	39	
Atezolizumab	0	6	
Durvalumab	0	2	
Preexisting autoimmune disease	1	7	0.29

There were no significant differences in age, gender, performance status (PS), treatment cycles, follow-up period, tumor type, prior therapy lines, type of PD-1/PD-L1 blockade administered, and preexisting autoimmune disease among the two groups

ANA antinuclear antibodies, *PS* performance status, *NSCLC* non-small cell lung carcinoma, *MM* malignant melanoma, *RCC* renal cell carcinoma

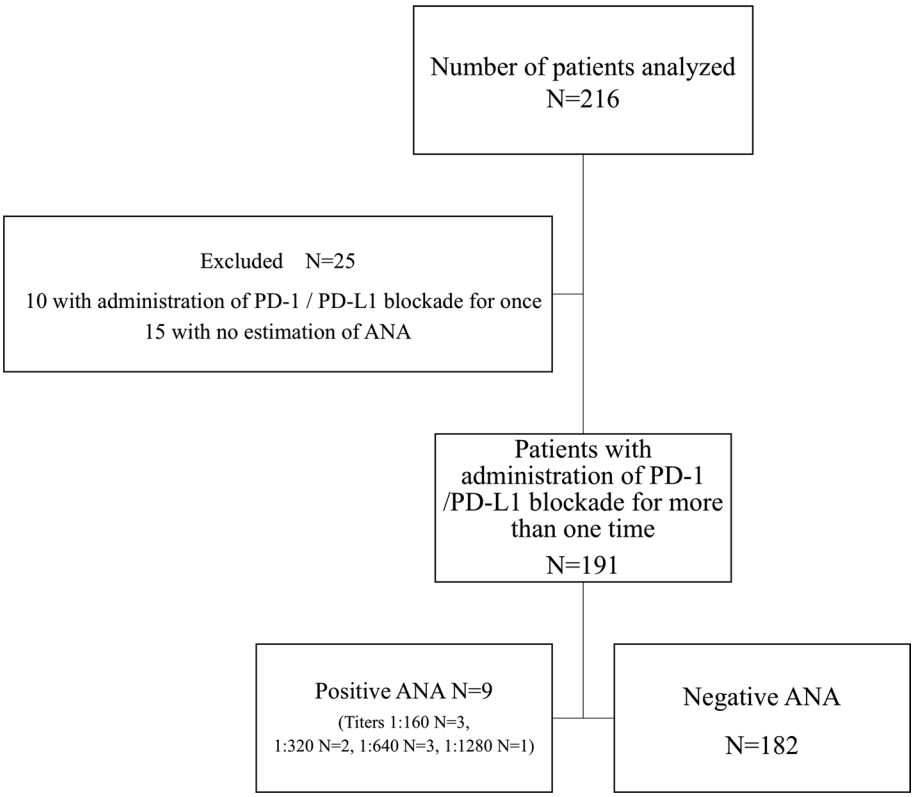

Fig. 1 Schematic depicting the subjects treated with PD-1/PD-L1 blockade who were examined in this study. Patients were classified into two groups according to the titers of antinuclear antibodies. Serum dilution of 1:160 were used for cutoff

Table 2 Development of irAEs among the positive and negative ANA groups

	Positive ANA $N=9$	Negative ANA $N=182$	*P* value
Total of irAEs	4	69	0.69
Thyroid Dysfunction	1 (Gr2: $N=1$)	27 (Gr1: $N=12$, Gr2: $N=15$)	0.76
Cutaneous disorders	2 (Gr1: $N=1$, Gr2: $N=1$)	33 (Gr1: $N=31$, Gr2: $N=2$)	0.76
Interstitial pneumonitis	1 (Gr2: $N=1$)	11 (Gr1: $N=5$, Gr2: $N=5$, Gr3: $N=1$)	0.54
Colitis	2 (Gr1: $N=1$, Gr2: $N=1$)	3 (Gr2: $N=2$, Gr3: $N=1$)	0.0002
Hypophysitis	1 (Gr3: $N=1$)	5 (Gr2: $N=2$, Gr3: $N=3$)	0.16
Diabetes	0	3 (Gr4: $N=3$)	0.70

Four patients in the positive ANA group and 69 patients in the negative ANA group developed any irAEs of any grade while showing no significant difference between the two groups. The presence of positive ANA was significantly higher in patients who developed colitis than in patients who did not

ANA antinuclear antibodies, *Gr* grade

group and 69 patients in the negative ANA group developed any irAEs of any grade while showing no significant difference between the two groups. Analysis for irAEs showed no significant difference in the development of cutaneous disorders, thyroid dysfunction, interstitial pneumonitis, hypophysitis, and diabetes. Interestingly, the presence of positive ANA was significantly higher in patients who developed colitis (2/9) than in patients who did not (3/182, $P=0.002$). A similar trend was also seen when a positive ANA cutoff at 1:80 and 1:40 serum dilution was used (Data are shown in Table S1, S2). One of the two patients with immunosuppressive therapy at baseline developed thyroid dysfunction and one did not develop any irAEs, which did not influence the above data.

Among the two patients who developed colitis in the positive ANA group, the staining pattern of ANA was homogeneous or speckled. Both the patients had grade 1–2 colitis and did not require corticosteroids or discontinuation of PD-1 blockade. A patient of MM without pre-existing ANA developed grade 3 colitis which required corticosteroid and discontinuation of nivolumab (Table 3).

Table 3 Clinical features of the patients who developed colitis induced by PD-1/PD-L1 blockade

Case	Age	Gender	Tumor type	Treatment	ANA titers	Staining pattern of ANA	Grade of colitis	Time to onset (week)	Requirement of corticosteroid	Discontinuation of PD-1/PD-1 blockade
1	73	M	NSCLC	Pembrolizumab	1:640	Homogeneous and speckled	2	10	(−)	(−)
2	80	M	NSCLC	Nivolumab	1:640	Speckled	1	7	(−)	(−)
3	70	F	NSCLC	Pembrolizumab	1:80	Homogenous and speckled	2	50	(−)	(−)
4	55	F	MM	Nivolumab	< 1:40	(−)	2	7	(−)	(−)
5	77	F	MM	Nivolumab	1:40	Speckled	3	18	(+)	(+)

Both patients with preexisting ANA had grade 1 or 2 colitis and did not require corticosteroids or discontinuation of PD-1 blockade

ANA antinuclear antibodies, *NSCLC* non-small cell lung carcinoma, *MM* malignant melanoma

Table 4 lists the clinical features and courses of all eight patients with preexisting autoimmune disease in this study. Autoimmune diseases which are closely related to ANA, such as SLE, Sjögren's syndrome, mixed connective tissue disease (MCTD), scleroderma, dermatomyositis, and polymyositis were not induced by PD-1/PD-L1 blockade. Three out of eight patients developed mild irAEs which were determined to be independent from their autoimmune disease and were managed without difficulty. However, a patient with dermatomyositis who had 1:80 serum dilution ratio experienced an exacerbation 17 days after induction of atezolizumab, which required an increase in corticosteroid and permanent discontinuation of atezolizumab. No other exacerbations of autoimmune disease were observed in this study.

Efficacy of treatment

ORR and DCR were estimated among the two groups. In the positive ANA group, one patient (12.5%) had a complete response, no patient had a partial response, two patients (25.0%) had stable disease, and five patients (62.5%) developed progressive disease. In the negative ANA group, 2 patients (1.3%) showed complete response, 38 patients (25.2%) had partial response, 62 patients (41.0%) had stable disease, and 49 patients (32.5%) developed progressive disease. The ORR in the positive and negative ANA groups was 12.5% and 26.5%, respectively, and showed no significant difference ($P = 0.38$, Fig. 2a). DCR was 37.5% in the positive ANA group and 67.5% in the negative group and did not reach statistical significance although showed a trend towards better efficacy in patients without ANA. ($P = 0.08$, Fig. 2b) However, this was not seen when a cutoff at 1:80 and 1:40 serum dilution was used for positive ANA (data are shown in Figure S1, S2).

Discussion

PD-1/PD-L1 blockade for cancer immunotherapy has revolutionized cancer treatment over the last several years; however, various issues of irAEs remain unclear. Clinical biomarkers which predict the occurrence of irAEs have not yet been identified. In this study, we evaluated the association between preexisting ANA and the development of irAEs, and describe the safety and efficacy of PD-1/PD-L1 blockade in patients with preexisting ANA. To our knowledge, this is the first study to evaluate this topic in multiple advanced cancers.

Our data showed no significant difference in the development of irAEs between the positive and negative ANA groups. Autoimmune diseases which are closely related to ANA such as SLE, Sjögren's syndrome, MCTD,

Table 4 Clinical features of the patients with preexsiting autoimmune disease

Case	Age	Gender	Tumor type	Treatment	ANA titers	Autoimmune disease	Baseline treatment	Worsening of autoimmune disease	Development of irAEs
1	35	F	MM	Nivolumab	1:320	UC	5-ASA	(−)	(−)
2	72	F	NSCLC	Pembrolizumab	1:80	Sjögren's syn	(−)	(−)	(+) cutaneous disorders
3	70	M	NSCLC	Atezolizumab	1:80	Dermatomyositis	PSL	(+)	(−)
4	82	M	Head and neck	Nivolumab	< 1:40	PMR	(−)	(−)	(−)
5	81	F	MM	Nivolumab	< 1:40	Sarcoidosis	(−)	(−)	(+) thyroid dysfunction
6	79	F	NSCLC	Nivolumab	< 1:40	RA	PSL immunosuppressant	(−)	(+) thyroid dysfunction
7	69	M	Head and neck	Nivolumab	1:40	Sarcoidosis	(−)	(−)	(−)
8	53	F	NSCLC	Pembrolizumab	1:40	Basedow disease	Potassium iodide	(−)	(−)

A patient with dermatomyositis had an exacerbation after induction of atezolizumab, which required an increase in corticosteroid and permanent discontinuation of atezolizumab

ANA antinuclear antibodies, *irAEs* immune-related adverse events, *NSCLC* non-small cell lung carcinoma, *MM* malignant melanoma, *UC* ulcerative colitis, *PMR* polymyalgia rheumatica, *RA* rheumatoid arthritis, *5-ASA* 5-aminosalicylic acid, *PSL* prednisolone

scleroderma, dermatomyositis, and polymyositis were not newly induced in both groups. However, one patient with preexisting dermatomyositis had an exacerbation after initiation of atezolizumab. No correlations were found between preexisting ANA and the development of cutaneous disorders, thyroid dysfunction, interstitial pneumonitis, hypophysitis, and diabetes. In contrast, there was a close relationship between preexisting ANA and the development of subsequent colitis. Comparable results were shown when we used a cutoff of ANA titers 1:40 and 1:80. We also estimated the efficacy of PD-1/PD-L1 therapy among the two groups and found no significant differences. Cancer treatment with PD-1/PD-L1 blockade seemed to provide similar levels of benefit to the two groups.

Previous studies have reported that severe and fatal irAEs may occur occasionally with the use of ICIs [12–14]. Some studies showed an association of the development of irAEs with durable responses and better prognoses in patients with NSCLC and MM [15–19]. Recently, we also reported that thyroid dysfunction induced by PD-1 blockade was correlated with better efficacy in patients with advanced malignancies [20]. Considering these results, early detection and management of irAEs are essential for optimal use of these drugs. Therefore, predictors for risk of developing irAEs are eagerly awaited and were investigated in other studies. For instance, changes in interleukin-17, clonal expansion of $CD8^+$ T cells, neutrophil activation markers, and eosinophil counts during cancer immunotherapy were related to irAEs, but these were not predictable factors at baseline [21–23]. In recent studies, Toi et al. and Yoneshima et al. showed that the incidence of irAEs did not significantly differ between positive and negative ANA patients with NSCLC, which are similar to our results [24, 25]. Moreover, the former study indicated no association between the presence of ANA and clinical efficacy of PD-1 treatments, while the later suggested poor outcome of such treatments in patients with ANA, thus clinical efficacy of PD-1 treatment in these patients remains controversial.

Recent studies revealed that some antibodies were related to specific irAEs. Osorio et al. and Hashimoto et al. [19, 26] showed that preexisting antithyroid antibodies were highly correlated to subsequent thyroid dysfunction. Suzuki et al. [27] reported that preexisting antibodies to the acetylcholine receptor were closely related to the development of myasthenia gravis. Interestingly, our data showed that preexisting ANA was correlated with the development of colitis. Perhaps, there may be an unknown specific autoantibody which induces colitis. A previous study reported that $CD8^+$ T cells were predominant in biopsies of anti-PD-1 induced colitis suggesting the role of $CD8^+$ T cells in anti-PD-1 induced colitis [28]; however, little is known about the precise immunological pathogenesis and further investigation is required. It is reported that the frequency and severity of colitis seem to be lower in anti-PD1 therapy than in anti-CTLA-4 therapy [29], although careful consideration is warranted in patients with preexisting ANA. Nevertheless, both cases of colitis with positive ANA were mild, manageable, and did not require corticosteroids or discontinuation of PD-1/PD-L1 therapy. To our knowledge, we are the first to report a correlation between positive ANA and colitis; however, a larger number of patients and a longer period of observation are needed to validate this association.

A number of studies show the safety of ICIs in patients with preexisting autoimmune diseases [13, 30–32]. These

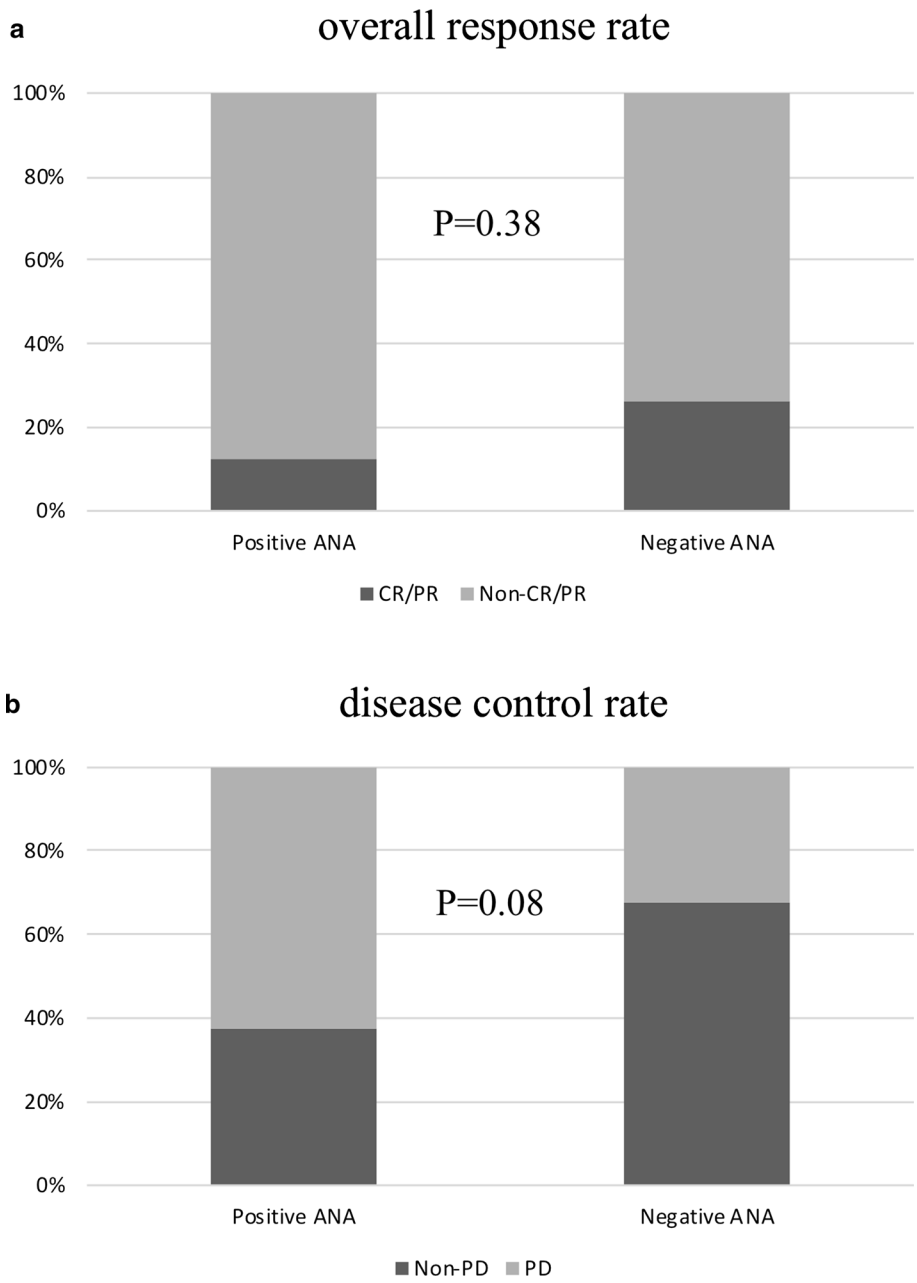

Fig. 2 Association between the efficacy of PD-1/PD-L1 treatment and the presence of antinuclear antibodies (ANA) at baseline. Overall response rate (ORR) and disease control rate (DCR) were estimated among the positive and negative ANA groups. ORR in the positive and negative ANA groups was 12.5% and 26.5%, respectively, which did not show a significant difference ($P=0.38$, **a**). DCR was 37.5% in the positive ANA group and 67.5% in the negative group which did not reach statistical significance although demonstrated a trend for better efficacy in patients without ANA. ($P=0.08$, **b**)

studies conclude that in patients with preexisting autoimmune diseases, ICIs could be considered with close monitoring since irAEs and exacerbations were often mild, easily managed and ICIs were as effective in these patients as in patients without autoimmune disease. Danlos et al. reported that an elevated risk of irAEs was found, although Menzies et al. showed a similar rate of irAEs compared to clinical trials. According to these results, the risk of irAEs in patients with preexisting autoimmune disease remains controversial. In addition, exacerbation of underlying autoimmune disease was reported frequently in patients with an active disease than in patients in remission [33]. In the present study, three patients developed mild irAEs which did not show noticeable difference compared to the patients without autoimmune disease. The patient with preexisting active dermatomyositis, with an ANA titer of 1:80, had an exacerbation requiring discontinuation of PD-L1 therapy and increase in corticosteroids. Because of the limited number of cases, a correlation between preexisting ANA and exacerbation of the autoimmune disease is difficult to suggest, however, it is essential that close monitoring is required in patients with preexisting autoimmune disease and ANA.

This study has some limitations. First, there was an inherent selection bias; this study reflects patients whose clinicians were willing to treat and severe cases of autoimmune disease with preexisting ANA may have been

underrepresented. Although the rate of positive ANA was similar to that of previous studies, we believe that this bias has a small influence on our study [10]. Second, the difference in irAEs observed between preexisting and non-preexisting ANA groups might be influenced by monitoring bias. Subsequent irAEs might be reported more frequently and rigidly in patients with preexisting ANA. Third, this study is limited by its retrospective nature and the patient sample size was relatively small. However, results from the present study may serve as a basis for future research.

Conclusion

In conclusion, no elevated risk of development in total irAEs was found in patients with preexisting ANA. However, subsequent colitis may occur frequently in patients with preexisting ANA. Therefore, with close monitoring and adherence to irAE treatment algorithms, safer treatment and similar levels of benefit can be anticipated. To provide relevant patient care and maximize the therapeutic benefits of ICIs, further studies are needed to identify the predictors of irAEs.

Author contributions TS, TI, YI and KT were responsible for the design of the study, selection and analysis and interpretation of the data. They also have revised critically the manuscript for important intellectual content. TI, YC, SH, JU, YT, SK, JA, TN, AA, HT, TK, HK, MM, HY, FH, MI, SH, OU, TT and KT were responsible for the acquisition and clinical interpretation of the data. All authors had full access to all of the data in the study and had final responsibility for the decision to submit for publication.

Funding No donations or supports exist for this study.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest. No donations or supports exist for this study.

Ethical approval The study was designed under the responsibility of Kyoto Prefectural University of Medicine, in conjunction with the steering committee.

Informed consent Given the retrospective nature of this work, informed consent was waived for the individual participants included in the study in accordance with the standards of the Kyoto Prefectural University of Medicine Institutional Medical Ethics Review Committee.

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