Original Article

A real-world retrospective study of incidence and associated factors of endocrine adverse events related to PD-1/PD-L1 inhibitors

Zhiyi Wang[1,2#], Chunyan Hu[1,2#], Anmei Zhang[1,2#], Xinxin Wang[1,2], Dong Zeng[1,2], Tao Long[1,2], Bo Zhu[1,2], Zhongyu Wang[1,2]

[1]Institute of Cancer, Xinqiao Hospital, the Third Military Medical University, Chongqing, China; [2]Chongqing Key Laboratory of Immunotherapy, Chongqing, China

Contributions: (I) Conception and design: Zhiyi Wang, A Zhang; (II) Administrative support: B Zhu; (III) Provision of study materials or patients: A Zhang, Zhiyi Wang, X Wang, D Zeng, T Long; (IV) Collection and assembly of data: A Zhang, Zhiyi Wang, C Hu; (V) Data analysis and interpretation: A Zhang, C Hu, Zhiyi Wang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Zhongyu Wang, MD, PhD. Institute of Cancer, Xinqiao Hospital, the Third Military Medical University, Chongqing 400037, China. Email: zhongyu655@163.com.

Background: The adverse events (AEs) related to immune checkpoint inhibitors (ICIs) have been mostly described in clinical trials, however, such trials are restricted to selection criteria and the results cannot wholly represent the real-world setting. We aimed to evaluate the real-world endocrine AEs associated with programmed death receptor-1/programmed death ligand-1 (PD-1/PD-L1) inhibitors in Chinese population.

Methods: This retrospective study included cancer patients who were treated with PD-1/PD-L1 inhibitors between January 2018 and December 2020 at Xinqiao Hospital, the Third Military Medical University. The information of 581 patients was reviewed, and data on clinical characteristics, PD-1/PD-L1 use, occurrence of endocrine AEs, and response to PD-1 blockade treatment were collated. The definition of endocrine AEs relied on diagnostic tests. Fisher's exact test or Pearson's chi-squared test was used to analyze the associations between endocrine variables and several categorical variables. Multivariate analyses were performed using a logistic regression model.

Results: Endocrine AEs were observed in 116 of the 581 patients (20.0%). The median time to onset of endocrine AEs was approximately 12 weeks. Pembrolizumab was associated with a significantly higher incidence of endocrine AEs compared to other anti-PD-1 agents (38.5%; P=0.0002); PD-1/PD-L1 inhibitor treatment combined with antiangiogenic therapy or with two other therapies (chemotherapy and antiangiogenic therapy) was associated with a significantly increased occurrence of endocrine AEs, compared to PD-1 blockade treatment alone (41.2%; P=0.015), both based on multivariate analysis. Patients who developed endocrine AEs had significantly higher overall response rates (ORRs; 33.3% *vs.* 23.1%, P=0.045) and disease control rates (DCRs; 91.1% *vs.* 79.1%, P=0.008) compared to patients without endocrine AEs. In multivariate analysis, endocrine AEs remained an independent factor for both ORR (OR: 1.764, 95% CI: 1.052–2.957, P=0.031) and DCR (OR: 2.896, 95% CI: 1.324–6.332, P=0.008) after adjusting for the confounding factors.

Conclusions: A real-world Chinese population receiving PD-1/PD-L1 treatment, pembrolizumab administrated and triple therapy treatment modalities had a higher incidence of endocrine AEs. Patients who developed endocrine AEs demonstrated a favorable response to PD-l blockade treatment.

Keywords: Programmed death receptor-1/programmed death ligand-1 (PD-1/PD-L1) inhibitors; endocrine adverse events (AEs); real-world evidence; cancer

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Introduction

In recent years, immune checkpoint inhibitors (ICIs) have rapidly gained popularity as promising therapeutics for multiple malignancies (1). ICIs target immune checkpoints, such as CTLA-4, programmed death receptor-1 (PD-1), and programmed death ligand-1 (PD-L1), and block the immunosuppressive ability of tumor cells, which enhances immune system activity and results in antitumor effects.

The CTLA-4 and PD-1 pathways play an important role in autoimmune tolerance and in the prevention of autoimmune diseases. Therefore, while attacking tumors, an overactivated immune system may also cause autoimmune-like clinical manifestations in the body's various organ systems. These manifestations are typically referred to as immune-related adverse events (irAEs) (2,3). Endocrine adverse events (AEs) are some of the most common irAEs. Although most endocrine AEs are mild to moderate (4,5), they may be life-threatening to patients if not recognized and discovered early (6,7). As ICIs are increasingly used in clinical settings, it is crucial to understand and recognize the associated irAEs, especially endocrine AEs.

Although many studies have reported ICI-related endocrine toxicity, most of these data are derived from clinical trials (8,9), but there is short of data in real world. Clinical trials are limited by strict inclusion and exclusion criteria and the results can only reflect a small subset of population. Patients in real-world situation are more complicated and heterogeneous. Therefore, gathering real-world evidence is helpful to answer clinical questions and fill the knowledge gaps.

In addition, reports of PD-1 blockade-related endocrine AEs have increased, largely from studies of anti-PD-1/PD-L1 monotherapy, followed by combined anti-CTLA-4 therapy, but studies based on PD-1 blockade combined with other traditional therapies, such as chemotherapy and antiangiogenic therapy, are rare. Nevertheless, studies on endocrine AEs in the Chinese population and PD-1/PD-L1 inhibitors manufactured in China as well as data on PD-l/PD-L1 blockade combined with other treatment modalities are scarce. Therefore, this current study evaluated the incidence of endocrine AEs and the association between endocrine AEs and the efficacy of PD-1 blockade treatment in cancer patients in a real-world Chinese population. We present the following article in accordance with the STROBE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-5459/rc).

Highlight box

Key findings

- This study found that a real-world Chinese population receiving PD-1/PD-L1 inhibitor treatment, pembrolizumab administrated and triple therapy treatment modalities had a higher incidence of endocrine adverse events. Patients who developed endocrine AEs demonstrated a favorable response to PD-l blockade treatment.

What is known and what is new?

- Many studies have reported PD-1/PD-L1 inhibitor-related endocrine toxicity, yet most of these data are derived from clinical trials.
- The spectrum of endocrine AEs in a real-world Chinese population and domestic drugs is unclear.

What is the implication, and what should change now?

- This study may provide clues for clinicians to strengthen monitoring and preventive management of endocrine AEs in higher risk patients.

Methods

Study design and patients

A retrospective review was conducted on all cancer patients who received anti-PD-1/PD-L1 monotherapy or combined therapy between January 2018 and December 2020 at Xinqiao Hospital, the Third Military Medical University. The follow-up rate was 100%. The last follow-up date was July 31, 2021. Patients were considered eligible for analysis if they satisfied the following criteria: (I) patients had pathologically confirmed malignant tumors; (II) patients completed at least two cycles of immunotherapy; and (III) detailed data on endocrine AEs were available.

Electronic medical records were used to collate detailed patient information, including age, sex, cancer type, stage, treatment lines, therapeutic regimens, treatment modality, and response to treatment. The drugs used in this study include antibodies targeting PD-1 (pembrolizumab, nivolumab, camrelizumab, toripalimab, tislelizumab, and sintilimab) and PD-L1 (atezolizumab and durvalumab).

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of Xinqiao Hospital, the Third Military Medical University (No. 2018-YANDI-082-01). Individual consent for this retrospective analysis was waived.

Endocrine AEs and evaluation of efficacy

Endocrine AEs included hyperglycemia, subclinical hypothyroidism, clinical-primary hypothyroidism, thyrotoxicosis, primary adrenal insufficiency, central hypothyroidism, and hypophysitis, in accordance with the guidelines for the management of immunotherapy-related toxicities (10,11). The time to onset was defined as the time from the first cycle of immunotherapy to the occurrence of endocrine AEs. Patients with AEs were divided into two groups, namely, the endocrine AE group and the nonendocrine AE group.

The objective tumor responses were assessed by investigators according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and included complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). CR plus PR was categorized as the objective response rate (ORR), while CR, PR, plus SD was defined as the disease control rate (DCR).

Statistical analysis

The percentage method was used for categorical variables and characteristics of endocrine AEs. Fisher's exact test or Pearson's chi-squared test was used to analyze the associations between endocrine variables and several categorical variables. Multivariate analyses were performed using a logistic regression model to calculate the odds ratio (OR) and 95% confidence interval (CI). The variables with a P value <0.05 identified in univariable analysis were selected for the multivariable analysis. All tests were performed with GraphPad Prism 8.0 software (GraphPad Software Inc., San Diego, CA, USA) or with the SPSS 18.0 software package (SPSS Inc., Chicago, IL, USA). A P value <0.05 was considered statistically significant.

Results

Patient characteristics

A total of 581 patients with various malignancies who received anti-PD-1/PD-L1 therapy were enrolled in this study. The median age was 57 years (range, 13–92 years), and most patients were male (n=425, 73.1%). Of the multiple tumor types included in this study, lung cancer was the most common (n=280, 48.2%) followed by digestive tract cancer (n=120, 20.7%). A total of 566 (97.4%) patients received anti-PD-1 agent therapy, and only 15 (2.6%) patients received anti-PD-L1 drugs. The majority of patients were administrated with domestic PD-1/PD-L1 inhibitors (n=480, 82.6%). Lines of treatment ranged from first-line to multiple-line treatment. Among the patients, 116 (20.0%) were screened for available data on endocrine AEs. The baseline characteristics are outlined in *Table 1*.

No significant differences were observed in sex, age, cancer stage, cancer type, lines of immunotherapy treatment, nor drug targets between the endocrine AE group and the nonendocrine AE group. However, differences in anti-PD-1 agent and treatment modality, which were both independent factors verified by a multivariate analysis, were found between patients with and without endocrine AEs (P<0.05). Detailed baseline clinical characteristics of the patients are shown in *Table 1*.

Figure 1 shows the incidence of endocrine toxicity resulting from different anti-PD-1 regimens from various manufacturers and in different treatment modalities. Among the different anti-PD-1 agents, pembrolizumab was associated with a significantly higher incidence of endocrine AEs (38.5%), while the incidence of endocrine AEs caused by sintilimab (10.4%) was relatively low. Patients who received other anti-PD-1 agents, including nivolumab, camrelizumab, toripalimab, and tislelizumab, experienced moderate incidences of endocrine AEs of 28.6%, 17.7%, 17.3%, and 16.8%, respectively (*Figure 1A*). In addition, the incidence of endocrine AEs was also markedly different between treatment modalities (*Figure 1B*). Patients who received a PD-1/PD-L1 inhibitor combined with two other therapies appeared to have the highest percentage of endocrine AEs (41.2%), followed by patients treated with immunotherapy combined with antiangiogenic therapy (30.6%). The incidence of endocrine AEs was similar between patients who received monotherapy and patients on chemotherapy.

Characteristics of endocrine AEs during PD-1 blockade treatment

Endocrine adverse effects were persistent in 116 of the 581 patients (20.0%). The overall median time to onset of endocrine AEs from treatment initiation was approximately

Table 1 Clinical characteristics of cancer patients treated with immune checkpoint inhibitors (n=581)

Measured variables	Total (n=581)	Endocrine AE group (n=116)	Non endocrine AE group (n=465)	P value	P value*
Gender				0.108	
Male	425	78 (18.4)	347 (81.6)		
Female	156	38 (24.4)	118 (75.6)		
Age (years)				0.527	
≥65	164	30 (18.3)	134 (81.7)		
<65	417	86 (20.6)	331 (79.4)		
Type of drug				0.189	
Anti-PD-L1	15	5 (33.3)	10 (66.7)		
Anti-PD-1	566	111 (19.6)	455 (80.4)		
Anti-PD-L1 agents				0.119	
Atezolizumab	7	4 (57.1)	3 (42.9)		
Durvalumab	8	1 (12.5)	7 (87.5)		
Anti-PD-1 agents				0.001	0.002
Pembrolizumab	65	25 (38.5)	40 (61.5)	<0.0001	
Nivolumab	21	6 (28.6)	15 (71.4)	0.404	
Camrelizumab	175	31 (17.7)	144 (82.3)	0.311	
Toripalimab	156	27 (17.3)	129 (82.7)	0.279	
Tislelizumab	101	17 (16.8)	84 (83.2)	0.342	
Cindilimab	48	5 (10.4)	43 (89.6)	0.076	
Cancer types				0.653	
Head and neck cancer	59	16 (27.1)	43 (72.9)		
Lung cancer	280	54 (19.3)	226 (80.7)		
Digestive tract cancer	120	20 (16.7)	100 (83.3)		
Urinary tumor	44	9 (20.5)	35 (79.5)		
Gynecologic cancer	40	8 (20.0)	32 (80.0))		
Melanoma	20	6 (30.0)	14 (70.0)		
Others	18	3 (16.7)	15 (83.3)		
Stage				0.111	
I-II	13	2 (15.4)	11 (84.6)		
III	108	14 (13.0)	94 (87.0)		
IV	460	100 (21.7)	360 (78.3)		
Lines of immunotherapy				0.197	
1	281	56 (19.9)	225 (80.1)		
2	173	28 (16.2)	145 (83.8)		
≥3	109	29 (26.6)	80 (73.4)		
Others	18	3 (16.7)	15 (83.3)		

Table 1 (*continued*)

Table 1 (*continued*)

Measured variables	Total (n=581)	Endocrine AE group (n=116)	Non endocrine AE group (n=465)	P value	P value*
Treatment modality				0.012	0.015
Monotherapy	99	20 (20.2)	79 (79.8)	0.983	
Chemotherapy combined	368	67 (18.2)	301 (81.8)	0.098	
Antiangiogenic therapy combined	62	19 (30.6)	43 (69.4)	0.032	
Other combination therapy[a]	35	3 (8.6)	32 (91.4)	0.075	
Triple therapy[b]	17	7 (41.2)	10 (58.8)	0.030	

[a], immunotherapy combined with radiotherapy or TKI; [b], immunotherapy combined with chemotherapy and concurrent antiangiogenic therapy. P value based on the Pearson chi-squared test or the Fisher's exact test; P value* based on logistic regression analysis. AE, adverse event; PD-1, programmed death receptor-1; PD-L1, programmed death ligand-1; TKI, tyrosine kinase inhibitor.

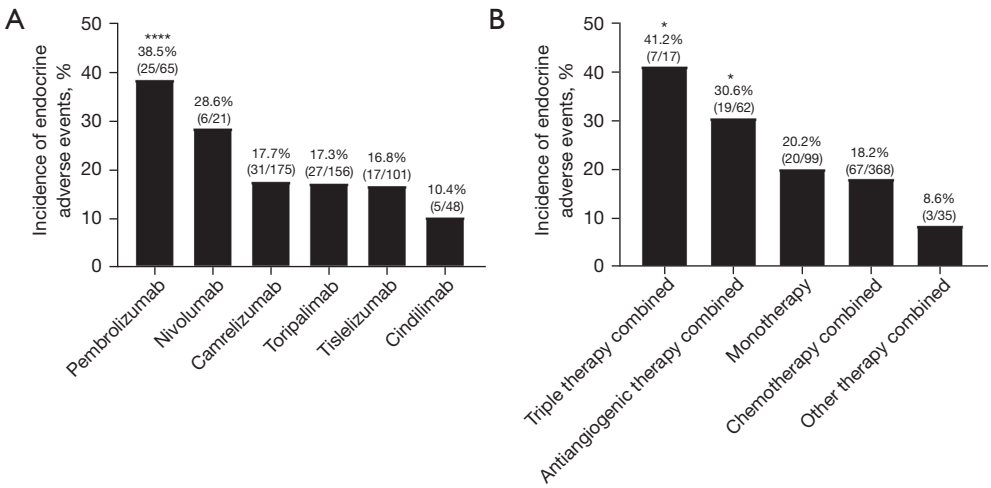

Figure 1 The incidence of endocrine adverse events in patients treated with anti-PD-1 agents from different manufacturers (A) and different treatment modalities (B). *, P<0.05; ****, P<0.0001. PD-1, programmed cell death protein-1.

12 weeks (range, 3–60 weeks). In this study, only one patient was found to experience hyperglycemia or central hypothyroidism and no primary adrenal insufficiency events were documented. Overall, 43 (37.1%) patients presented with clinical and primary hypothyroidism, 42 (36.2%) had subclinical hypothyroidism, 23 (19.8%) had thyrotoxicosis, and 6 (5.2%) experienced thyrotoxicosis. In 32 (27.6%) of these cases, disease or abnormal endocrine test values were detected before immunotherapy was administered. In addition, 12 (10.3%) patients simultaneously exhibited other irAEs during PD-1 blockade treatment. Among patients with endocrine toxicities, only 4 delayed immunotherapy, and 3 discontinued treatments. The characteristics of the endocrine AEs are shown in *Table 2*.

Response to PD-1 blockade treatment according to the development of endocrine AEs

The last follow-up timepoint was in June 2021. The response was evaluated in 458 of the 581 patients, including 90 patients in the endocrine AE group and 368 patients in the nonendocrine AE group. The efficacy analysis indicated that none of the patients achieved CR, 115 (25.1%) patients achieved PR, 258 (56.3%) patients maintained SD, and 85 (18.6%) patients had PD, which resulted in an ORR of 25.1% and a DCR of 81.4% (*Table 3*). The percentages of CR, PR, SD, and PD in patients in the endocrine AE and nonendocrine AE groups were 0%, 33.3%, 57.8%, and 8.9% *vs.* 0%, 23.1%, 56.0%, and 20.9%, respectively

(P=0.012; *Table 3*). Patients who developed endocrine AEs demonstrated a favorable response to PD-l blockade treatment compared with those without endocrine AEs. The univariate and multivariate analysis on ORR and DCR were presented respectively in *Table 4* and *Table 5*. In univariate analysis, the endocrine AE group had a significantly higher ORR (33.3% *vs.* 23.1%, P=0.045) and DCR (91.1% *vs.* 79.1%, P=0.008) compared to the nonendocrine AE group (*Figure 2A*,*2B*). In multivariate analysis, endocrine AEs remained an independent factor for both ORR (OR: 1.764, 95% CI: 1.052–2.957, P=0.031) and DCR (OR: 2.896, 95% CI: 1.324–6.332, P=0.008) after adjusting for the confounding factors.

Table 2 Characteristics of the endocrine adverse effects

Characteristics	Value
The time to onset (weeks), median [range]	12 [3–60]
Endocrine AE types, n (%)	
Hyperglycemia	1 (0.9)
Subclinical hypothyroidism	42 (36.2)
Clinical, primary hypothyroidism	43 (37.1)
Thyrotoxicosis	23 (19.8)
Primary adrenal insufficiency	0
Central hypothyroidism	1 (0.9)
Hypophysitis	6 (5.2)
With disease or abnormal test value of endocrine, n (%)	32 (27.6)
Impact on treatment, n (%)	
Delay	4 (3.4)
Discontinue	3 (3.4)
Complicated with other irAE, n (%)	12 (10.3)

AE, adverse event; irAE, immune-related adverse event.

Discussion

PD-1 blockade can lead to a wide spectrum of AEs, which are quite different from the AEs associated with traditional chemotherapy, radiotherapy, and molecular targeted therapy. These irAEs can affect numerous organs of the body, including the skin, liver, colon, lungs, and endocrine system, as well as less common sites, such as the kidneys, eyes, nervous system, cardiovascular system, musculoskeletal system, and hematologic system (11,12). Endocrine AEs are some of the most common irAEs. A previous study has revealed that approximately 5–10% of patients who receive ICIs are prone to endocrine AEs of any grade, with a median time to onset of 9 weeks (range, 5–36 weeks) from treatment initiation (13). In this study, endocrine AEs occurred in 116 (20.0%) patients with a median time to onset of 12 weeks (range, 3–60 weeks). This is likely to be an overestimation of the actual incidence of endocrine AEs. This may be due to a variety of reasons, including ethnic differences, diverse ICI manufacturers, and different therapeutic modalities. For example, in our study, a significant number of patients were treated with ICIs combined with other therapies. The time to onset of AEs was later than that in a prior study (12 *vs.* 9 weeks) (11), and the largest proportion was in eligible patients who completed at least two cycles of immunotherapy after we omitted partial cases that experienced endocrine AEs after the first cycle.

Previous studies have compared the incidence of endocrine AEs in different ICI regimens. It appears that

Table 3 Impact of endocrine adverse events on the efficacy of treatment

Tumor response	Total (n=458)	Endocrine AE group (n=90)	Non-endocrine AE group (n=368)	P
CR	0	0	0	0.012
PR	115 (25.1)	30 (33.3)	85 (23.1)	
SD	258 (56.3)	52 (57.8)	206 (56.0)	
PD	85 (18.6)	8 (8.9)	77 (20.9)	
ORR%	115 (25.1)	30 (33.3)	85 (23.1)	0.045
DCR%	373 (81.4)	82 (91.1)	291 (79.1)	0.008

P values <0.05 are considered statistically significant. AE, adverse event; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

Table 4 Univariate and multivariate analyses of clinical variables on ORR (n=458)

Variables	No.	ORR, n (%)	Univariate analyses		Multivariate analyses		
			χ^2	P value[a]	OR	95% CI	P value[b]
Gender			3.462	0.063			
Male	336	92 (27.4)					
Female	122	23 (18.9)					
Age (y)			0.325	0.569			
≥65	126	34 (27.0)					
<65	332	81 (24.4)					
Cancer types			19.283	0.004	0.857	0.772–1.016	0.075
Head and neck cancer	41	14 (34.1)					
Lung cancer	237	72 (30.4)					
Digestive tract cancer	90	8 (8.9)					
Urinary tumor	35	9 (25.7)					
Gynecologic cancer	27	6 (22.2)					
Melanoma	10	1 (10.0)					
Others	18	5 (27.8)					
Stage			3.235	0.198			
I–II	11	5 (45.5)					
III	81	23 (28.4)					
IV	366	87 (23.8)					
Lines of immunotherapy			21.881	0.000	0.598	0.454–0.787	0.000
1	227	77 (33.9)					
2	132	21 (15.9)					
≥3	66	15 (22.7)					
Others	33	2 (6.1)					
Type of drug			0.864	0.353			
Anti-PD-L1	14	5 (35.7)					
Anti-PD-1	444	110 (24.8)					
Treatment modality			9.301	0.054	0.830	0.615–1.121	0.224
Monotherapy	67	14 (20.9)					
Chemotherapy combined	301	88 (29.2)					
Antiangiogenic therapy combined	53	9 (17.0)					
Other combination therapy[c]	25	3 (12.0)					
Triple therapy[d]	12	1 (8.3)					
Endocrine AE			4.029	0.045	1.764	1.052–2.957	0.031
No	368	85 (23.1)					
Yes	90	30 (33.3)					

[a], P value based on the Pearson chi-squared test or the Fisher's exact test; [b], P value based on logistic regression analysis; [c], immunotherapy combined with radiotherapy or TKI; [d], immunotherapy combined with chemotherapy and concurrent antiangiogenic therapy. ORR, objective response rate; OR, odds ratio; PD-1, programmed death receptor-1; PD-L1, programmed death ligand-1; AE, adverse event; TKI, tyrosine kinase inhibitor.

Table 5 Univariate and multivariate analyses of clinical variables on DCR (n=458)

Variables	No.	DCR, n (%)	Univariate analyses			Multivariate analyses	
			χ^2	OR	P value[a]	95% CI	P value[b]
Gender			0.834	0.361			
Male	336	277 (82.4)					
Female	122	96 (78.7)					
Age (y)			0.412	0.512			
≥65	126	105 (83.3)					
<65	332	268 (80.7)					
Cancer types			16.212	0.013	0.787	0.673–0.921	0.003
Head and neck cancer	41	36 (87.8)					
Lung cancer	237	206 (86.9)					
Digestive tract cancer	90	66 (73.3)					
Urinary tumor	35	25 (71.4)					
Gynecologic cancer	27	20 (74.1)					
Melanoma	10	6 (60.0)					
Others	18	14 (77.8)					
Stage			3.723	0.155			
I–II	11	11 (100.0)					
III	81	69 (85.2)					
IV	366	293 (80.1)					
Lines of immunotherapy			14.164	0.003	0.702	0.550–0.896	0.005
1	227	200 (88.1)					
2	132	97 (73.5)					
≥3	66	52 (78.8)					
Others	33	24 (72.7)					
Type of drug			0.079	0.779			
Anti-PD-L1	14	11 (78.6)					
Anti-PD-1	444	362 (81.5)					
Treatment modality			13.423	0.009	0.958	0.727–1.262	0.760
Monotherapy	67	48 (71.6)					
Chemotherapy combined	301	258 (85.7)					
Antiangiogenic therapy combined	53	42 (79.2)					
Other combination therapy[c]	25	16 (64.0)					
Triple therapy[d]	12	9 (75.0)					
Endocrine AE			6.930	0.008	2.896	1.324–6.332	0.008
No	368	291 (79.1)					
Yes	90	82 (91.1)					

[a], P value based on the Pearson chi-squared test or the Fisher's exact test; [b], P value based on logistic regression analysis; [c], immunotherapy combined with radiotherapy or TKI; [d], immunotherapy combined with chemotherapy and concurrent antiangiogenic therapy. DCR, disease control rate; OR, odds ratio; PD-1, programmed death receptor-1; PD-L1, programmed death ligand-1; AE, adverse event; TKI, tyrosine kinase inhibitor.

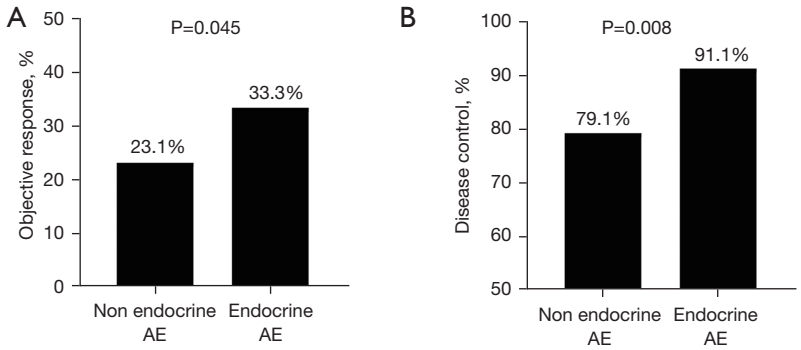

Figure 2 A comparison of the objective response rate (A) and the disease control rate (B) based on endocrine adverse events during anti-PD-1/PD-L1 treatment. AE, adverse event; PD-1, programmed death receptor-1; PD-L1, programmed death ligand-1.

treatment with PD-1/PD-L1 blockade therapy was more likely to result in fewer irAEs compared to treatment involving CTLA-4 blockade (14,15). This likely contributes to a more restricted repertoire of T cells that are affected by PD-1 blockade than by CTLA-4 blockade (14,16). However, to date, few studies have compared the toxicities of anti-PD-1 agents from different manufacturers. Our current study examined the endocrine AEs of anti-PD-1 antibodies produced by different manufacturers, and pembrolizumab was shown to be associated with a higher incidence of endocrine toxicities. As increasingly more anti-PD-1/PD-L1 antibodies are approved for the treatment of various malignancies, clinicians are likely to select agents with lower toxicity. Our report provides novel data for the selection of less toxic drugs, however, these conclusions should be further verified in multi-centered studies.

Amazingly, endocrine AEs are associated with traditional combined therapy modalities. Prior studies reported that the combination of two ICIs increased the risk of immunotherapy-related endocrinopathies (8,17). However, whether PD-1 blockade combined with other traditional therapies, such as chemotherapy and antiangiogenic therapy, contributes to endocrine AEs is unclear. In this study, patients who received immunotherapy in combination with two other therapy types appeared to have the highest percentage of endocrine AEs, the incidence of which was also significantly higher in patients treated with immunotherapy combined with antiangiogenic therapy. Monotherapy and combination chemotherapy have a similar incidence of endocrine AEs. This implies that we should consider the impact of increased endocrine toxicity in patients receiving certain combination therapies. Furthermore, monitoring and preventive management should be strengthened when potentially highly toxic combination treatment models are adopted.

Several studies have shown that irAE onset may be a clinical biomarker of the benefit of immunotherapies, including PD-1/PD-L1 inhibitors (18). Similarly, the development of immune-related endocrine events may also predict a better cancer response to immunotherapy in patients with specific cancer types (9,19-22). This current study included patients with various cancer types and also linked endocrine AEs to a better response to PD-1 blockade treatment. Although the primary pathophysiologic mechanism of immune-related endocrine AEs is still unclear, the occurrence of endocrine AEs indicates that the immune response is adequately activated, which not only results in cancer cell death and the induction of disease control, but also damage to normal tissue and the development of AEs (23). However, the confirmed association between irAEs and the effectiveness of immunotherapy remains to be explored.

This study is based on a real-world Chinese population treated with PD-1/PD-L1 inhibitors and comprehensively evaluated the incidence of endocrine AEs. We found differences among different ICI therapies and detected an association between AEs and efficacy. This study has several limitations. First, this is a retrospective study with data deviation. The severity of endocrine toxicity could not be evaluated due to the retrospective nature of the study. Second, this study was conducted at only one center, with limitations on cancer type and the anti-PD-1/PD-L1 drug spectrum. In addition, data on progression-free survival (PFS) and overall survival (OS) are lacking in our study, and

consequently, the association between endocrine AEs and survival in cancer patients could not be assessed.

Conclusions

This study demonstrated that the endocrine AEs associated with PD-1/PD-L1 inhibitors are different when anti-PD-1/PD-L1 drugs and combined therapy modalities were used and suggested that patients who developed endocrine AEs exhibited a better response to PD-l blockade treatments. These data are derived from a real-world Chinese population, and most of the drugs were manufactured in China, and thus, these results might better reflect actual clinical practice in China. This study may also provide clues for clinicians to strengthen monitoring and preventive management of endocrine AEs in higher risk patients. However, these conclusions should be confirmed in additional centers.

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Footnote

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