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ORIGINAL RESEARCH

Immune-Related Adverse Event-Related Adrenal Insufficiency Mediates Immune Checkpoint Inhibitors Efficacy in Cancer Treatment

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Purpose: Immune checkpoint inhibitors (ICIs) have significantly improved the outcomes of patients with cancer; however, these agents may initiate immune-related adverse events (irAEs). Previous studies have demonstrated a robust correlation between disease prognosis and the occurrence of irAEs, specifically skin or endocrine irAEs. Herein, we aimed to evaluate the correlation between irAE-related adrenal insufficiency (AI) and ICI treatment efficacy.

Patients and methods: Patients diagnosed with gastrointestinal, respiratory, head and neck, urological, skin and gynecologic cancers treated with anti-programmed cell death 1 (PD-1)/anti-programmed cell death ligand 1 (PD-L1) antibody as monotherapy or combined therapy (combined with chemotherapy or targeted therapy) were divided into irAE-A (patients with irAE-related AI), irAE-B (patients with other irAEs) and non-irAE groups. Immunotherapy efficacy was assessed based on the disease control rate (DCR), progression-free survival (PFS), and overall survival (OS). Survival probabilities were estimated using the Kaplan–Meier method with the log–rank test.

Results: Of the 192 patients enrolled in our study, 17 developed irAE-related AI and 83 developed other irAEs. The DCR of the irAE-A and irAE-B groups were higher than that of the non-irAE group ($P<0.05$). Multiple extended Cox regression analyses showed that irAE status (irAE-A vs non-irAE, $P=0.008$; irAE-B vs non-irAE, $P=0.020$), Eastern Cooperative Oncology Group (ECOG) status ($P=0.045$), tumor-node-metastasis (TNM) stage ($P=0.000$), and treatment line ($P=0.002$) were independent predictors of PFS. Contrarily, irAE status (irAE-A vs non-irAE, $P=0.009$; irAE-B vs non-irAE, $P=0.013$), ECOG status ($P=0.007$), TNM stage ($P=0.035$), treatment line ($P=0.001$) and treatment modality ($P=0.008$) were independent predictors for OS.

Conclusion: IrAE-related AI was significantly associated with ICI treatment efficacy in patients with cancer, which could be a potentially predictable marker. Due to the destruction of adrenal tissue by T cells with enhanced activity, AI reflects enhanced T cell activity to some extent.

Keywords: endocrine adverse event, malignancies, monoclonal antibody therapy, immune-related side effects, treatment efficacy

Introduction

Cancer treatment has been revolutionized with the recent emergence of immune checkpoint inhibitors (ICIs), which have significantly improved the treatment outcomes in different cancers, including melanoma, advanced non-small cell lung cancer (NSCLC), renal cell carcinoma, gastrointestinal cancer, urothelial carcinoma, and squamous cell carcinoma of the head and neck.[1–6] ICIs target immune checkpoints, such as cytotoxic T-lymphocyte antigen 4 (CTLA-4), programmed cell death 1 (PD-1), and programmed cell death ligand 1 (PD-L1) on immune or tumor cells to enhance the tumor-killing capability of immune cells such as CD8 T lymphocytes.[7] Immune related adverse events (irAEs) have been observed with ICI treatment, possibly as a consequence of the following mechanisms: increased T-cell activity against antigens

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present in tumors and healthy tissues, elevated levels of inflammatory cytokines or pre-existing autoantibodies, and enhanced complement-mediated inflammation owing to the direct binding of an anti-CTLA-4 antibody to CTLA-4 expressed on normal tissues.[7,8] IrAEs affect almost all organs, including the skin, gastrointestinal tract, lungs, liver, and endocrine and musculoskeletal systems with varying frequencies and severities.[9]

IrAEs have been shown to promote the efficacy of ICIs in patients with cancer. In patients with NSCLC, the occurrence of irAEs was associated with clinical benefits in terms of progression-free survival (PFS), while in those with gastric cancer, it was linked to improved PFS and overall survival (OS).[10,11] Grade 1–2 irAEs, particularly skin or endocrine irAEs, are also associated with prolonged PFS and OS in patients with melanoma.[12] We previously reported that irAEs, particularly low-grade irAEs such as endocrine, dermatological, or gastrointestinal irAEs, are a predictable marker for better ICI treatment efficiency in patients with hepatocellular carcinoma (HCC).[13]

IrAE-related adrenal insufficiency (AI) is an endocrine adverse event characterized by a malfunctioning hypothalamic-pituitary-adrenal axis and a subsequent deficiency of adrenal cortisol production. It is categorized into primary AI encompassing low serum cortisol levels and elevated plasma adrenocorticotropic hormone (ACTH) levels, and secondary AI, associated with isolated ACTH insufficiency and multiple pituitary hormone deficiency.[14] The incidence of AI in monotherapy ICI treatment was reported to be 0.7%, with a 0.2% incidence of grade 3 or above adverse events; however, the incidence of AI in combined ICI treatment increased to 4.2%.[15,16] AI manifests as non-specific symptoms including headache, fatigue, nausea, emesis, hypotension, and hypoglycemia, which may be overlooked by oncologists.[17] Patients with severe adrenal crisis characterized by shock caused by hypotension, disturbance of consciousness, and electrolyte disorders such as hyponatremia and hyperkalemia require long-term, even lifelong substitutive hormone replacements.[18] Patients with ICI-induced AI with lung cancer as the main tumor type achieved an objective response rate (ORR) of 70% and disease control rate (DCR) of 100%,[19] implying that irAE-related AI might be associated with favorable outcomes in ICI treatment. In the present study, we evaluated the correlation between irAE-related AI and ICI treatment efficacy in patients with cancer with gastrointestinal cancers as the main cancer type.

Methods

Patients

We retrospectively obtained data of 192 patients (esophageal, gastric, liver, biliary tract, lung, head and neck, kidney, endometrial, cervical, pancreatic, colon, thyroid, and bladder cancers, and melanoma) treated with anti-PD-1 antibody/anti-PD-L1 antibody monotherapy or combination therapy with chemotherapy or targeted drugs between February 2019 and February 2023 at the Fourth Hospital of Hebei Medical University. The inclusion criteria were: histopathology-confirmed malignant tumors before treatment initiation, received ICI treatment, detailed and complete clinical data, and no infectious inflammatory diseases. The exclusion criteria were: ICI treatment information combined with other tumor histories, infectious inflammatory diseases, patients who discontinued treatment or refused to accept assessment, and patients without complete medical information. All clinical data, including age, sex, cancer type, Eastern Cooperative Oncology Group Performance Status (ECOG PS), tumor-node-metastasis (TNM) stage, treatment lines, treatment modality, and irAE status, were collected for analysis. All procedures were performed in accordance with the Helsinki Declaration of 1964 and subsequent versions, reviewed and approved by the Ethics Committee of the Fourth Hospital of Hebei Medical University. Due to the retrospective nature of the study, informed consent was waived.

Treatment and Assessment

Patients received standard anti-PD-1 antibody/anti-PD-L1 antibody (monotherapy or combined with chemotherapy or targeted drugs) every 3 weeks until disease progression, clinical deterioration, unacceptable toxicity, or patient refusal. The immunotherapeutic drugs administered were pembrolizumab, camrelizumab, tislelizumab, sintilimab, toripalimab and durvalumab. Objective tumor response was evaluated using computed tomography (CT) or magnetic resonance imaging (MRI) scans repeated every 6–9 weeks according to the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1.[20] The endpoints were response time, PFS, and OS. OS was defined as the time from treatment initiation to death from any cause or study cut-off. DCR was defined as the percentage of patients who achieved complete

response, partial response, and stable disease. PFS was defined as the period from treatment initiation to the date of disease progression, death, or study cut-off. IrAEs were defined as inflammatory side effects caused by an imbalance in immunological tolerance owing to ICI treatment. IrAEs were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events ver.4.03 (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40). Patients were divided into irAE-A (patients with irAE-related AI), irAE-B (patients with other irAEs), and non-irAE groups. Diagnostic criteria for irAE-related AI were as follows: primary AI, defined as suspected clinical manifestations of adrenocortical hypofunction with low morning serum cortisol levels (<138 nmol/L) accompanied by increased plasma ACTH levels, excluding adrenal metastasis, bleeding, or infection; secondary AI, defined as low morning serum cortisol levels (<138 nmol/L) with low plasma ACTH levels (<5 pg/mL) and an inadequate response to a 250 mcg ACTH stimulation test with or without abnormal pituitary findings on MRI, excluding pituitary metastases, infectious pituitary diseases, and pituitary adenomas.[21,22]

Statistical Analysis

Statistical analyses were performed using SPSS software (version 24.0; SPSS Inc., Chicago, IL, USA). Differences between the groups were compared using the chi-square test or Fisher's exact test for categorical variables. Survival probabilities were estimated using the Kaplan–Meier method with the Log rank test. To address immortal time bias resulting from the time-dependent nature of irAE status, multivariable extended Cox regression models with irAE state as a time-dependent covariate were used to evaluate their impact on patient PFS and OS. Statistical significance was set at $P<0.05$.

Results

Patient Characteristics

In total, 192 patients (140 males) with a median age of 63 years (range 20–90 years) were included in the study.

Based on the National Cancer Institute Common Terminology Criteria for irAEs, 100 of 192 patients (52.1%) experienced irAEs, of which 17 (8.85%) experienced AI, including primary AI (1.56%) and secondary AI (7.29%). Patients were divided into irAE-A (patients with irAE-related AI), irAE-B (patients with other irAEs), and non-irAE groups according to the occurrence and category of irAEs to evaluate the impact of irAEs on treatment efficacy. Sixty-four patients had a good performance status (PS) of 0 or 1, whereas 128 had a poor PS of 2–4. The main cancer types were gastric cancer (50.00%), esophageal cancer (14.06%), HCC (12.50%), head and neck cancer (9.90%), and lung cancer (3.65%). Approximately, 81 and 111 patients belonged to stages I–III and □, respectively. Among these patients, 105 received a PD-1 inhibitor combined with chemotherapy, 56 received a PD-1 inhibitor combined with targeted drugs, 15 received a PD-1 inhibitor combined with both chemotherapy and targeted drugs, and 14 received a mono-PD-1 inhibitor. Two received PD-L1 inhibitors combined with chemotherapy. First-line therapy was administered to 133 patients, whereas 59 received second-line or later treatment. The detailed baseline clinical characteristics of the different groups are listed in Table 1.

IrAE-Related AI Mediates Treatment Efficacy of ICIs

The overall DCR of ICI treatment was 64.06% (123 patients), with 94.12% (16) in the irAE-A group, 72.29% (60) in the irAE-B group, and 51.09% (47) in the non-irAE group. The results revealed no statistically significant difference in DCR between the irAE-A and irAE-B groups ($P=0.065$); however, the DCR of both groups was significantly higher than that of the non-irAE group ($P<0.05$) (Table 2).

PFS was analyzed in 187 patients (97.40%) and OS in 179 patients (93.23%), with a median follow-up time of 645 days (range, 27–1126 days). The Kaplan–Meier curves of PFS and OS among the groups are presented in Figure 1. The median PFS of the irAE-A group was not reached, but was significantly longer than that of the irAE-B group at 264 days (95% confidence interval [CI]: 213–315 days, $P=0.001$) and the non-irAE group at 116 days (95% CI: 61–171 days, $P=0.000$). The PFS of the irAE-B group was also longer than that of the non-irAE group ($P=0.005$). The median OS of 860 days (95% CI: 577–1143 days) for the irAE-A group was significantly longer than the median OS of 491 days (95%

Table 1 Characteristics of Patients with Different Types of irAEs or Without irAEs

Variable	irAE-A Group No. (%)	irAE-B Group No. (%)	Non-irAE Group No. (%)	*p*-value
Gender				0.635
Male	11 (64.7)	60 (72.3)	69 (75.0)	
Female	6 (35.3)	23 (27.7)	23 (25.0)	
Age				0.278
<65	11 (64.7)	49 (59.0)	45 (48.9)	
≥65	6 (35.3)	34 (41.0)	47 (51.1)	
ECOG PS				0.099
≤1	8 (47.1)	32 (38.6)	24 (26.1)	
>1	9 (52.9)	51 (61.4)	68 (73.9)	
TNM				0.053
I–III	7 (41.2)	43 (51.8)	31 (33.7)	
IV	10 (58.8)	40 (48.2)	61 (66.3)	
Treatment line				0.465
1	14 (82.4)	57 (68.7)	62 (67.4)	
>1	3 (17.6)	26 (31.3)	30 (32.6)	
Cancer type				0.025
Esophageal cancer	5 (29.4)	7 (8.4)	15 (16.3)	
Gastric cancer	6 (35.3)	37 (44.6)	53 (57.6)	
Hepatocellular cancer	2 (11.8)	17 (20.5)	5 (5.4)	
Biliary tract cancer	0 (0.0)	2 (2.4)	0 (0.0)	
Respiratory cancer	1 (5.9)	3 (3.6)	3 (3.3)	
Others	3 (17.6)	17 (20.5)	16 (17.4)	
Treatment modality				0.296
ICI combined therapy	17 (100.0)	74 (89.2)	87 (94.6)	
Monotherapy	0 (0.0)	9 (10.8)	5 (5.4)	

Abbreviations: irAE, immune-related adverse event; irAE-A group, patients with irAE-related adrenal insufficiency; irAE-B group, the group with other irAEs; PS, performance status.

Table 2 Response to Immunotherapy of Cancer Patients

Comparison	PD	SD	PR	CR	DCR (%)	*p*-value
irAE-A group vs irAE-B group						0.065
irAE-A group	1	14	2	0	94.1% (95% CI: 71.3–99.9%)	
irAE-B group	23	53	6	1	72.3% (95% CI: 62.5–2.1%)	
irAE-A group vs Non-irAE group						0.001
irAE-A group	1	14	2	0	94.1% (95% CI: 71.3–99.9%)	
Non-irAE group	45	38	9	0	51.1% (95% CI: 40.7–61.5%)	
irAE-B group vs Non-irAE group						0.004
irAE-B group	23	53	6	1	72.3% (95% CI: 62.5%-82.1%)	
Non-irAE group	45	38	9	0	51.1% (95% CI: 40.7%-61.5%)	

Abbreviations: irAE, immune-related adverse event; irAE-A group, patients with irAE-related adrenal insufficiency; irAE-B group, the group with other irAEs; PD, progressive disease; SD, stable disease; PR, partial response; CR, complete response; DCR, disease control rate.

CI: 331–651 days, *P*=0.004) for the irAE-B group and 302 days (95% CI: 203–401 days, *P*=0.000) for the non-irAE group. The OS of the irAE-B group was also longer than that of the non-irAE group (*P*=0.000) (Figure 1A and B).

In the univariate analysis of PFS and OS with clinical characteristics including sex, age, ECOG status, TNM stage, treatment line, cancer type, treatment modality and irAE status as covariates, irAE status (PFS: irAE-A vs non-irAE, *P*=0.000; irAE-B vs non-irAE, *P*=0.005; irAE-A vs irAE-B, *P*=0.003; OS: irAE-A vs non-irAE, *P*=0.000; irAE-B vs non-

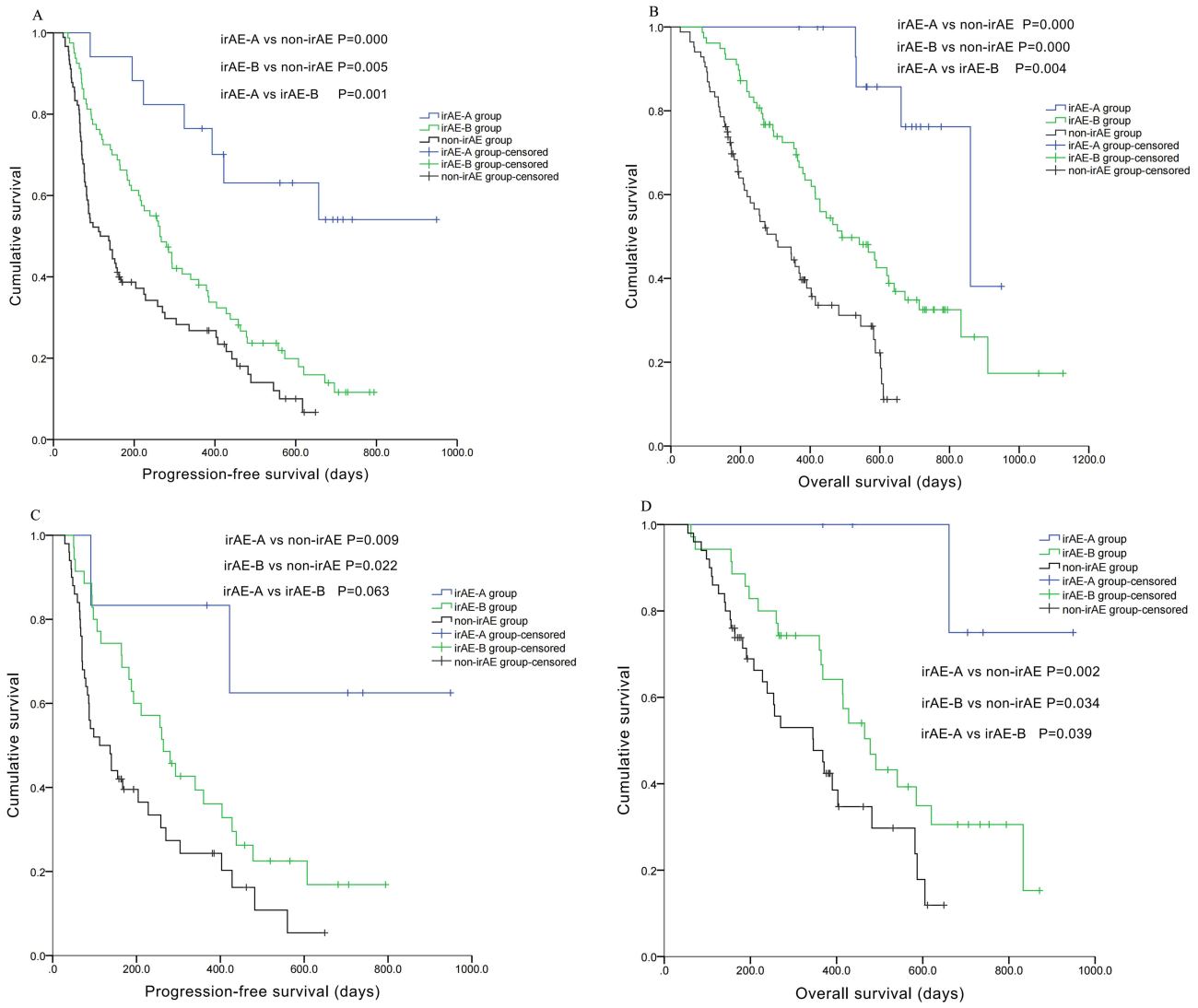

Figure 1 Association between irAE status and prognosis of patients. (**A**) The Kaplan-Meier curve of progression-free survival (PFS) in cancer patients. (**B**) The Kaplan-Meier curve of overall survival (OS) in cancer patients. (**C**) The Kaplan-Meier curve of progression-free survival (PFS) in patients with gastric cancer. (**D**) The Kaplan-Meier curve of overall survival (OS) in patients with gastric cancer.

irAE, *P*=0.000; irAE-A vs irAE-B, *P*=0.009), ECOG status (PFS: *P*=0.017; OS: *P*=0.000), TNM stage (PFS: *P*=0.000; OS: *P*=0.007), and treatment line (PFS: *P*=0.000; OS: *P*=0.000) were significantly associated with PFS and OS, whereas sex, age, cancer type and treatment modality had no significant effect on PFS and OS (*P*>0.05) (Table 3).

Finally, we performed multiple extended Cox regression analyses with covariates of age, sex, ECOG status, TNM stage, treatment line, cancer type, treatment modality, and time-dependent covariates of irAE status as covariates to account for immortal time bias and identify independent prognostic factors for PFS and OS. As presented in Table 3, the irAE status (irAE-A vs non-irAE, *P*=0.008; irAE-B vs non-irAE, *P*=0.020; irAE-A vs irAE-B, *P*=0.005), ECOG status (*P*=0.045), TNM stage (*P*=0.000), and treatment line (*P*=0.002) were independent predictors of PFS, whereas irAE status (irAE-A vs non-irAE, *P*=0.009; irAE-B vs non-irAE, *P*=0.013; irAE-A vs irAE-B, *P*=0.008), ECOG status (*P*=0.007), TNM stage (*P*=0.035), treatment line (*P*=0.001) and treatment modality (*P*=0.008) were independent predictors for the OS.

Owing to the sample size for other cancer types, we performed further subgroup analysis for only 96 patients with gastric cancer. The detailed baseline clinical characteristics of the subgroups are listed in Table 4, with no statistical

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Table 3 Univariate and Multiple Extended Cox Regression Model on PFS and OS in Cancer Patients

Covariate	PFS						OS					
	Univariate Analysis (n=187)			Multivariate Analysis (n=187)			Univariate Analysis (n=179)			Multivariate Analysis (n=179)		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Gender												
Male	Reference			Reference			Reference			Reference		
Female	0.965	0.670–1.390	0.848	0.993	0.684–1.441	0.969	1.181	0.783–1.783	0.427	1.184	0.776–1.807	0.433
Age												
<65	Reference			Reference			Reference			Reference		
≥65	1.045	0.754–1.450	0.790	1.033	0.729–1.463	0.855	1.200	0.814–1.769	0.356	1.280	0.839–1.955	0.252
ECOG PS												
≤1	Reference			Reference			Reference			Reference		
>1	1.543	1.079–2.205	0.017	1.462	1.008–2.120	0.045	2.321	1.469–3.668	0.000	1.954	1.204–3.172	0.007
TNM												
I–III	Reference			Reference			Reference			Reference		
IV	1.874	1.330–2.641	0.000	2.015	1.372–2.958	0.000	1.737	1.161–2.600	0.007	1.620	1.034–2.539	0.035
Treatment line												
1	Reference			Reference			Reference			Reference		
>1	1.846	1.309–2.603	0.000	1.737	1.222–2.471	0.002	2.123	1.432–3.149	0.000	2.021	1.319–3.097	0.001
Cancer type												
Gastrointestinal cancers	Reference			Reference			Reference			Reference		
Respiratory cancer	1.345	0.547–3.306	0.519	0.976	0.393–2.427	0.959	0.715	0.260–1.960	0.514	0.604	0.219–1.662	0.329
Others	1.114	0.743–1.669	0.602	1.095	0.723–1.659	0.669	1.020	0.639–1.628	0.934	0.771	0.467–1.274	0.310
Treatment modality												
ICI combined therapy	Reference			Reference			Reference			Reference		
Monotherapy	1.286	0.711–2.323	0.405	1.633	0.862–3.093	0.133	1.755	0.914–3.373	0.091	2.686	1.298–5.558	0.008
irAEs												
Non-irAE group	Reference			Reference			Reference			Reference		
irAE-A group	0.187	0.085–0.411	0.000	0.003	0.000–0.210	0.008	0.113	0.040–0.317	0.000	0.000	0.000–0.059	0.009
irAE-B group	0.613	0.436–0.862	0.005	0.095	0.013–0.686	0.020	0.440	0.291–0.664	0.000	0.006	0.000–0.336	0.013

Abbreviations: PFS, progression-free survival; OS, overall survival; PS, performance status; irAEs, immune-related adverse events; irAE-A group, patients with irAE-related adrenal insufficiency; irAE-B group, the group with other irAEs; HR, hazard ratio; CI, confidence interval.

Table 4 Characteristics of Gastric Cancer Patients Among Different Groups

Variable	irAE-A Group No. (%)	irAE-B group No. (%)	Non-irAE group No. (%)	*p*-value
Gender				0.413
Male	3 (50.0)	26 (70.3)	40 (75.5)	
Female	3 (50.0)	11 (29.7)	13 (24.5)	
Age				0.272
<65	5 (83.3)	21 (56.8)	26 (49.1)	
≥65	1 (16.7)	16 (43.2)	27 (50.9)	
ECOG PS				0.064
≤1	1 (16.7)	18 (48.6)	14 (26.4)	
>1	5 (83.3)	19 (51.4)	39 (73.6)	
TNM				0.851
I–III	2 (33.3)	14 (37.8)	13 (24.5)	
IV	4 (66.7)	23 (62.2)	40 (75.5)	
Treatment line				1.000
1	4 (66.7)	23 (62.2)	34 (64.2)	
>1	2 (33.3)	14 (37.8)	19 (35.8)	
Treatment modality				0.757
ICI combined chemotherapies	4 (66.6)	26 (70.3)	32 (60.4)	
ICI combined targeted drugs	1 (16.7)	8 (21.6)	12 (22.6)	
ICI combined chemotherapies and targeted drugs	1 (16.7)	3 (8.1)	9 (17.0)	

Abbreviations: irAE, immune-related adverse event; irAE-A group, patients with irAE-related adrenal insufficiency; irAE-B group, the group with other irAEs; PS, performance status.

Table 5 Response to Immunotherapy in Gastric Cancer Patients

Comparison	PD	SD	PR	CR	DCR (%)	*p*-value
irAE-A group vs irAE-B group						1.000
irAE-A group	1	4	1	0	83.3% (95% CI: 35.9–99.6%)	
irAE-B group	8	25	3	1	78.4% (95% CI: 64.5–92.3%)	
irAE-A group vs Non-irAE group						0.228
irAE-A group	1	4	1	0	83.3% (95% CI: 35.9–99.6%)	
Non-irAE group	24	26	3	0	54.7% (95% CI: 40.9–68.6%)	
irAE-B group vs Non-irAE group						0.021
irAE-B group	8	25	3	1	78.4% (95% CI: 64.5–92.3%)	
Non-irAE group	24	26	3	0	54.7% (95% CI: 40.9–68.6%)	

Abbreviations: irAE, immune-related adverse event; irAE-A group, patients with irAE-related adrenal insufficiency; irAE-B group, the group with other irAEs; PD, progressive disease; SD, stable disease; PR, partial response; CR, complete response; DCR, disease control rate.

differences. No difference in DCR was observed between irAE-A and irAE-B (P=1.000) or irAE-A vs non-irAE (P=0.228); however, the DCR of the irAE-B group was higher than that of the non-irAE group (P=0.021) (Table 5).

PFS and OS were analyzed in the 91 patients. The Kaplan–Meier curves of PFS among the groups showed that the median PFS of the irAE-A group was higher than that of the non-irAE group (P=0.009), but not higher than that of the irAE-B group (P=0.063). The PFS in the irAE-B group was longer than that in the non-irAE group (P=0.022). The median OS of the irAE-A group was longer than those of both the irAE-B (P=0.039) and non-irAE (P=0.002) groups, and the OS of the irAE-B group was also longer than that of the non-irAE group (P=0.034) (Figure 1C, Figure 1D). The irAE status (PFS: irAE-A vs non-irAE, P=0.012; irAE-B vs non-irAE, P=0.024; irAE-A vs irAE-B, P=0.087; OS: irAE-A vs non-irAE, P=0.015; irAE-B vs non-irAE, P=0.028; irAE-A vs irAE-B, P=0.069) was significantly associated with PFS and OS in the univariate analysis, but no statistical difference was observed in the multiple extended Cox regression analyses of irAE status (Table 6).

Table 6 Univariate and Multiple Extended Cox Regression Model on PFS and OS in Gastric Cancer Patients

Covariate	PFS						OS					
	Univariate Analysis (n=91)			Multivariate Analysis (n=91)			Univariate Analysis (n=91)			Multivariate Analysis (n=91)		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Gender												
Male	Reference			Reference			Reference			Reference		
Female	1.093	0.648–1.843	0.738	0.998	0.571–1.745	0.995	1.157	0.651–2.057	0.620	1.392	0.756–2.562	0.289
Age												
<65	Reference			Reference			Reference			Reference		
≥65	0.952	0.588–1.539	0.839	1.013	0.590–1.741	0.961	1.222	0.711–2.101	0.468	1.730	0.907–3.301	0.096
ECOG PS												
≤1	Reference			Reference			Reference			Reference		
>1	1.146	0.701–1.874	0.587	0.980	0.576–1.670	0.942	1.229	0.702–2.151	0.471	1.048	0.539–2.037	0.890
TNM												
I–III	Reference			Reference			Reference			Reference		
IV	1.744	1.009–3.015	0.047	1.114	0.596–2.084	0.735	1.828	0.960–3.483	0.066	1.296	0.620–2.708	0.490
Treatment line												
1	Reference			Reference			Reference			Reference		
>1	2.525	1.529–4.171	0.000	2.454	1.255–4.799	0.009	2.880	1.675–4.953	0.000	2.328	1.166–4.647	0.017
Treatment modality												
ICI combined chemotherapies	Reference			Reference			Reference			Reference		
ICI combined targeted drugs	3.170	1.783–5.637	0.000	2.470	1.137–5.368	0.022	3.199	1.753–5.839	0.000	2.258	1.065–4.788	0.034
ICI combined chemotherapies and targeted drugs	3.202	1.579–6.492	0.001	3.228	1.461–7.133	0.004	2.902	1.361–6.185	0.006	1.774	0.685–4.591	0.237
irAEs												
Non-irAE group	Reference			Reference			Reference			Reference		
irAE-A group	0.160	0.038–0.672	0.012	0.007	0.000–8.523	0.172	0.082	0.011–0.612	0.015	0.006	0.000–316.532	0.354
irAE-B group	0.563	0.342–0.928	0.024	0.184	0.007–4.723	0.306	0.525	0.296–0.932	0.028	0.144	0.001–23.901	0.457

Abbreviations: PFS, progression-free survival; OS, overall survival; PS, performance status; irAEs, immune-related adverse events; irAE-A group, patients with irAE-related adrenal insufficiency; irAE-B group, the group with other irAEs; HR, hazard ratio; CI, confidence interval.

Discussion

Hypophysitis has various subtypes, including AI, secondary hypothyroidism, prolactin deficiency, growth hormone deficiency, and secondary hypogonadism. Previous data have demonstrated mixed results on the association between hypophysitis (including the subtypes above) and outcomes of cancers, mainly melanoma and lung cancer.[23–26] However, in this study, we only focused on primary AI and the hypophysitis subtype of AI (secondary AI) on ICI treatment efficacy. We found that AI was related to the efficacy of ICIs in cancer treatment, which differs from the findings of previous studies on the relationship between hypophysitis and cancer outcomes. Additionally, we demonstrated that irAE-related AI was associated with better outcomes in patients with cancer, particularly gastrointestinal tumors. A study of patients with advanced HCC treated with ICIs showed that one of five patients with long-term survival developed AI.[27] All three responders in the Phase II DART study (SWOG S1609) for breast cancer treated with ICIs developed AI.[28] The ORR and DCR were 70% and 100%, respectively, in cancer patients with ICI-induced AI with lung cancer as the main tumor type.[19] These results support the hypothesis that irAE-related AI promotes ICI efficacy in patients with cancer.

The incidence of irAE-related AI reported here was higher than that in previous studies, probably because of the non-specific symptoms of AI overlooked by oncologists.[14,15] Routine examinations for cortisol and pituitary function, and clinical education on hypotension, hypoglycemia, and apathy, must be performed before initiation of ICI therapy. As irAE-related AI exhibits a superior capacity for predicting cancer treatment efficacy, promptly identifying and treating irAE-related AI is crucial to ensure efficient and uninterrupted ICI therapy, thereby benefiting more patients with cancer.

Different doses and administration regiments of hormones may have different outcomes on different tumors, with some studies reporting that hormones change treatment efficacy, whereas others do not.[29,30] We used a physiological substitution amount (≤30 mg) of hydrocortisone for AI treatment; this low-dose glucocorticoids (7.5 mg prednisone) had good OS.

To date, no consensus has been reached on the possible mechanisms underlying irAE-related AI.[31] Upon ICI treatment, pre-existing autoreactive helper CD4+ and cytotoxic CD8+ T cells may be activated, subsequently infiltrating and destroying the adrenal cortex.[18] AI-associated autoantibodies such as anti-21-hydroxylase autoantibody and anti-guanine nucleotide-binding protein G(olf) subunit alpha antibodies have been reported to be present in patients with irAE-related AI.[31–33] Cross-reactive T and B cells activated by the ectopic expression of tissue antigens from tumor cells following ICI treatment may attack both tumor cells and the adrenal or pituitary glands.[31] The efficiency of ICI treatment is mainly achieved by activated cytotoxic T cells, organ damage by autoreactive B cell autoantibodies initiated under T-cell activation, and abnormally enhanced T-cell activity in both the pituitary and adrenal glands, which may largely explain the increased treatment efficacy for irAE-related AI in patients with cancer. In future studies, an immunohumanized animal model will be used to explore the mechanism of AI-mediated ICI treatment efficacy.

This study has some limitations. First, this was a single-center retrospective study, and data from multiple centers should be evaluated in future studies. Second, the sample size was relatively limited, which may have led to wider confidence intervals that may have affected our results. The sample size limited our subgroup analysis for each cancer type, even for the gastric cancer cohort, which was the largest sample size among our patients. An increased effect of irAE status on treatment efficiency was observed in the subgroup univariate analysis of gastric cancer but not in multiple analysis. The small sample size of patients with gastric cancer might have limited the accuracy of the statistical analysis. In further, we will utilize a larger sample size to explore the relationship between irAE-related AI and the treatment efficacy of ICIs in gastric cancer. Nonetheless, our findings reveal a relationship between irAE-related AI and ICI treatment efficacy in patients with cancer. This pilot study provides a foundation for future research with larger sample sizes.

Conclusion

IrAE-related AI was significantly associated with ICI treatment efficacy in patients with cancer as a potentially predictable marker. AI can reflect enhanced T-cell activity to some extent following the destruction of adrenal tissue by T cells with enhanced activity.

Data Sharing Statement

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

Ethical Statement

All procedures were performed in accordance with the Helsinki Declaration of 1964 and subsequent versions and were reviewed and approved by the Ethics Committee of the Fourth Hospital of Hebei Medical University. The study was conducted retrospectively, and some patients were deceased at the commencement of the study. Moreover, our data did not contain any personally identifiable patient information and underwent strict confidentiality measures during the data collection process. Due to these aforementioned factors, the need for written informed consent was waived by the ethics committee of the Fourth Hospital of Hebei Medical University.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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