Original Article

Association of concomitant H1 antihistamine and immune checkpoint inhibitor therapy on survival outcome and safety in patients with advanced primary lung cancer: a cohort study

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Background: Antihistamines alleviate the side effects of antitumor drugs and exert antitumor effects. This study aimed to investigate the potential impact of short-term concomitant use of antihistamines with immune checkpoint inhibitor (ICI) therapy on the efficacy and immune-related adverse events (irAEs) of immunotherapy for patients with advanced lung cancer.

Methods: We retrospectively analyzed the medical records of 211 patients diagnosed with advanced primary lung cancer and treated with immunotherapy at Tianjin Medical University Cancer Institute and Hospital between January 1, 2018, and January 1, 2022. Among these patients, 109 who received H1 antihistamine during the infusion of anti-programmed cell death-1 (PD-1) and anti-programmed cell death ligand 1 (PD-L1) antibodies were assigned to the experimental group; meanwhile, the remaining 102 patients who did not receive H1 antihistamines were assigned to the control group. Balancing was achieved through inverse probability of treatment weight (IPTW) estimation. The data were analyzed using Kaplan-Meier curves and Cox regression analyses.

Results: The median progression-free survival (mPFS) was 12.7 months in the experimental group and 4.3 months in the control group, while the median overall survival (mOS) was 32.8 months in the experimental group and 18.1 months in the control group. In the experimental group, patients treated with only H1 antihistamines had longer mPFS and mOS compared with those who received H1 plus H2 antihistamines. Similarly, in the control group, patients who did not receive antihistamines had a longer mPFS and mOS than those who only received H2 antihistamines. After conducting multivariate analyses, we found that H1 and H2 antihistamines were respectively identified as good and poor independent prognostic factors for both progression-free survival (PFS) and overall survival (OS). The rates of irAEs in the experimental and control groups were 52.4% and 69.2%, respectively, and grade ≥3 irAEs occurred in 4.5% and 25.9% of patients, respectively.

Conclusions: Concomitant use of H1 antihistamines can improve immunotherapy efficacy and reduce

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irAEs. Meanwhile, concomitant use of H2 antihistamines is associated with reduced PFS and OS time.

Keywords: Diphenhydramine; immune checkpoint inhibitors (ICIs); lung cancer; safety; efficacy

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Introduction

Lung cancer accounts for 11.6% of the total 18.1 million cancer cases and 18.4% of the 9.5 million total cancer-related deaths each year worldwide (1). The continual development in treatment methods based on novel drugs has benefited many patients with cancer. The approach of combining immunotherapy targeting programmed cell death-1 (PD-1) and its ligand (PD-L1) with established chemotherapies has transformed the first-line treatment of advanced lung cancer (2). In recent years, the US Food and Drug Administration (FDA) has approved numerous drugs targeting the PD-1/PD-L1 pathway for the treatment of lung cancer, either as single agents or in combination with other therapies (3).

Highlight box

Key findings

- This study showed that the concurrent administration of H1 antihistamines and immunotherapy is associated with enhanced survival benefits and prolonged progression-free survival (PFS). In contrast, the concurrent use of H2 antihistamines is associated with reduced PFS and overall survival (OS) in patients with lung cancer.

What is known and what is new?

- Histamine and H1 receptors play a crucial role in the tumor microenvironment. Concomitant use of antihistamines and immune checkpoint inhibitors (ICIs) may enhance the effect of ICIs.
- Concurrent administration of H1 antihistamines and immunotherapy is associated with enhanced survival benefits and prolonged PFS. Meanwhile, concurrent use of H2 antihistamines is associated with reduced PFS and OS.

What is the implication, and what should change now?

- These findings suggest the potential utility of low-cost H1 antihistamines as adjuvant therapy in combination with immunotherapy for more effectively and safely treating patients with lung cancer.

Patients with cancer often receive antitumor drugs in combination with other adjuvant drugs, which may impact the efficacy of systemic therapy due to potential drug interactions (4). Existing data indicate a higher rate of tumor progression in patients treated with corticosteroids. In contrast, nonsteroidal anti-inflammatory drug use at the initiation of nivolumab treatment has a positive effect on the objective response rate (5). Moreover, aspirin intake has been correlated with a decreased mortality rate in patients treated with immunotherapy (6). When combined with chemotherapy, antihistamines have either inhibitory or promoting effects depending on certain cancer type. H1 antihistamines, such as loratadine, have been associated with improved survival among patients with immunogenic tumors, such as lung cancer (7). However, their combination with other therapies, particularly immunotherapy, has not been extensively studied (8). Animal experiments indicated that H1 antihistamines could restore T-cell function suppressed by cancer cell–secreted or allergy-released histamines and improve the efficacy of immunotherapies, such as immune checkpoint blockade (6).

Antihistamines are typically used for the prevention or treatment of adverse gastrointestinal reactions, such as allergies, nausea, and vomiting, during antitumor therapy (8,9). However, how the short-term concomitant use of antihistamines and ICIs affects the efficacy and immune-related adverse events (irAEs) of tumor immunotherapy needs to be further explored. Developing new drugs and improving current treatment protocols are vital for increasing efficacy, overcoming resistance, and reducing the side effects of treatments. Therefore, we retrospectively analyzed patients who received concomitant antihistamines during immunotherapy to assess the safety and effectiveness of antihistamines in patients undergoing immunotherapy for lung cancer. We present this article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-795/rc).

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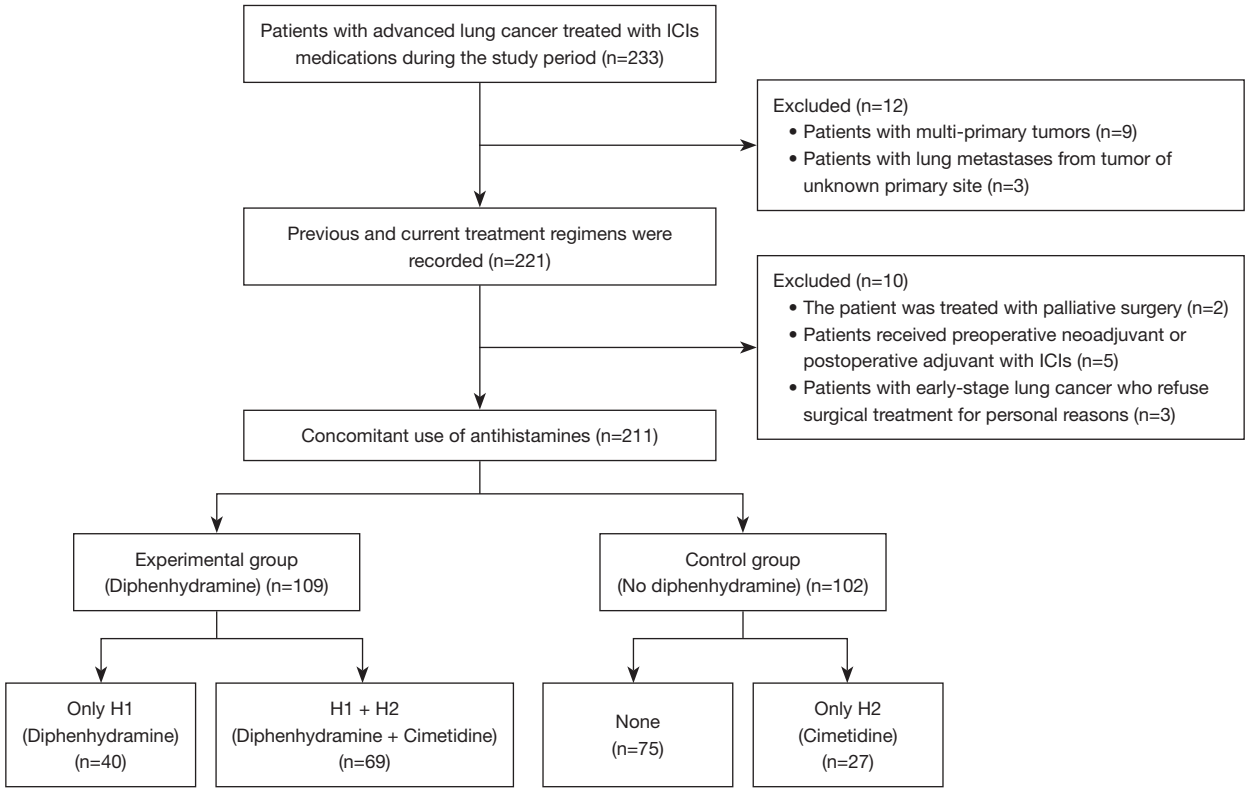

Figure 1 Flowchart of the patients included in the study. ICIs, immune checkpoint inhibitors.

Methods

Patient population

We retrospectively analyzed the medical records of 211 patients diagnosed with advanced primary lung cancer, confirmed pathologically or radiographically, and treated with immunotherapy at Tianjin Medical University Cancer Institute and Hospital between January 1, 2018, and January 1, 2022. Individuals in the experiment were not randomized into groups because this was deemed irrelevant to this study. The main inclusion criteria for patients were as follows: age ≥18 years old, with unresectable stage III or recurrent/metastatic stage IV primary lung cancer, ineligible for surgical treatment after multidisciplinary consultation, treated with immunotherapy, and adequate organ function. The main exclusion criteria included lung metastases from other malignancies, another primary malignancy, and perioperative adjuvant therapy (*Figure 1*).

Among the 211 patients screened, 109 patients who received H1 antihistamines during the infusion of anti-PD-1/PD-L1 therapy were assigned to the experimental group; meanwhile, the remaining 102 patients who did not receive H1 antihistamines were assigned to the control group. All patients treated with H1 antihistamines continued to use them throughout the immunotherapy cycle.

Clinical and pathological characteristics, such as age, sex, Karnofsky Performance Scale (KPS) score, tumor type and stage, radiotherapy history, surgical history, type of ICI used, number of treatment lines, occurrence and grade of irAEs, and concomitant use of antihistamines, were recorded. Among the patients in the experimental group, 69 received both the H1 antihistamine diphenhydramine and the H2 antihistamine cimetidine, while 40 received only diphenhydramine. In the control group, 27 patients received cimetidine only, and 75 received neither diphenhydramine nor cimetidine. Antihistamines should be administered 30 minutes prior to the administration of immunotherapy drugs. All patients signed an informed consent form before immunotherapy and agreed to their data being used for the study. This study was conducted in compliance with the ethical principles of the Declaration of Helsinki (as revised in 2013) and was approved by the review board of the Ethics Committee of Tianjin Medical University Cancer Institute

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and Hospital (No. E20241045).

Follow-up and evaluation

Patients received regular follow-up, with intervals of 6 weeks for the first year and 8 weeks thereafter, as well as periodic assessments from initial treatment to June 30, 2023. Before administration of each dose, the following assessments were completed: routine serum blood, liver, and kidney biochemistry; coagulation tests; thyroid function tests; cortisol levels; and cardiac markers. Other examinations that were performed as appropriate included chest, head, neck, abdominal, and pelvic computed tomography (CT) scans; abdominal and neck ultrasound; positron emission tomography-CT; and emission CT.

Evaluation of efficacy

The primary endpoint was progression-free survival (PFS) according to the Response Evaluation Criteria in Solid Tumors version 1.1. PFS was defined as the time from the first immunotherapy to disease progression, death from any cause, or the follow-up deadline. The secondary endpoint was overall survival (OS), which was calculated from the date of initial treatment to the follow-up deadline or death.

irAE assessment

Adverse events (AEs) and abnormal laboratory discoveries were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. If patients who received ICIs or ICIs in combination with chemotherapy experienced AEs, AEs were further diagnosed as irAEs or non-irAEs by a multidisciplinary team including an oncologist, rheumatologist, immunologist, radiologist, and pathologist. IrAEs were managed by a multidisciplinary team throughout the whole process.

Statistical analysis

Continuous variables are expressed as the mean and standard deviation (SD) or as the median and interquartile range (IQR), while categorical variables are expressed as frequency distributions (n, %). Differences in baseline characteristics between the two groups were estimated using the chi-square test (*Table 1*). Differences were also estimated using standardized differences (d value), which allowed for estimation of the eventual imbalance between treatment groups regardless of their size: d values <0.1 indicated a negligible difference, d values between 0.1 and 0.3 indicated small differences, d values between 0.3 and 0.5 indicated moderate differences, and d values >0.5 indicated large differences.

The propensity score (PS) is the probability of treatment assignment conditional on observed baseline characteristics (10). The PS was calculated to represent the likelihood of receiving H1 antihistamines conditional on the covariates in this study. All available clinical and tumor variables, when treatment started, were used for PS calculation to avoid incurring a possible imbalance of other parameters not correlated with the probability of receiving H1 antihistamines but with unknown effects on the outcome. The obtained PS was then used to generate a stabilized inverse probability of treatment weight (IPTW) (11) analysis through appropriate mathematical calculations, which was then used to weigh each clinical feature and the measured outcomes of each patient in both groups. After weighting, the baseline characteristics and d-values were recalculated, and an adequate balance was declared if all variables returned to d<0.1. Once the weighted pseudo-population of patients was obtained, the differences between the outcomes of the concomitant application of H1 receptor antagonists during the administration of ICIs were analyzed. IPTW-adjusted Kaplan-Meier curves were calculated to compare survival among groups graphically. Survival analyses were performed using IPTW-adjusted log-rank and Cox regression analyses. Event rate analyses (AE incidence) were completed using an IPTW-adjusted generalized linear model with natural logarithm transformation. The results are expressed as hazard ratios (HRs) or rate ratios. No priori significance level was set for the analyses. The analysis was repeated for each subgroup. Statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA).

Prognostic factors associated with PFS and OS were analyzed (*Tables 2*,*3*). Univariate and multivariate analyses using IPTW-adjusted log-rank and Cox regressions were conducted in all patients for factors including concomitant medications (diphenhydramine and cimetidine) and all baseline characteristics, such as age, sex, KPS score, pathological pattern, TNM stage, history of radiotherapy and surgery, number of immune-oncology (IO) lines, type of IO drug, and combination therapies (combined, radiation, anti-vascular, or cell therapies).

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Table 1 Baseline characteristics of the study population after IPTW adjustment

Variables	Experimental group (n=106.1)	Control group (n=106.8)	P value	d value
Age (years)				
≤60	63.2 (59.6)	60.5 (56.6)	0.66	0.060
>60	42.9 (40.4)	46.3 (43.4)		
Sex				
Male	76.5 (72.1)	81.9 (76.8)	0.43	0.106
Female	29.6 (28.0)	24.8 (23.3)		
KPS score				
≤80	34.8 (32.8)	37.5 (35.2)	0.72	0.049
>80	71.3 (67.2)	69.2 (64.9)		
Pathological pattern				
SCC	41.1 (38.7)	42.5 (39.8)	>0.99	0.022
AC	50.0 (47.1)	48.7 (45.6)		0.030
SCLC	14.1 (13.3)	14.7 (13.8)		0.014
Other	1.0 (0.9)	0.9 (0.9)		
TNM stage				
III	92.1 (86.8)	95.3 (89.3)	0.57	0.075
IV	14.0 (13.2)	11.4 (10.7)		
History of radiotherapy				
Yes	18.9 (17.8)	21.3 (19.9)	0.69	0.052
No	87.2 (82.2)	85.5 (80.1)		
History of surgery				
Yes	14.0 (13.2)	14.4 (13.5)	0.93	0.010
No	92.2 (86.9)	92.3 (86.5)		
Number of IO lines				
1	52.7 (49.6)	50.4 (47.2)	0.93	0.050
2	33.5 (31.6)	35.2 (33.0)		0.028
≥3	19.9 (18.8)	21.2 (19.8)		
Type of IO drug				
Anti-PD-1	98.9 (93.2)	100.0 (93.6)	0.89	0.018
Anti-PD-L1	7.3 (6.8)	6.8 (6.4)		
Combined cimetidine				
Yes	51.3 (48.4)	50.8 (47.6)	0.90	0.018
No	54.8 (51.6)	56.0 (52.5)		
Combined chemotherapy				
Yes	71.7 (67.5)	73.6 (69.0)	0.82	0.032
No	34.4 (32.5)	33.1 (31.0)		

Table 1 (*continued*)

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Table 1 (*continued*)

Variables	Experimental group (n=106.1)	Control group (n=106.8)	P value	d value
Combined radiotherapy				
Yes	3.4 (3.2)	2.4 (2.3)	0.67	0.053
No	102.7 (96.8)	104.4 (97.8)		
Combined anti-vascular therapy				
Yes	19.3 (18.2)	21.4 (20.0)	0.73	0.044
No	86.8 (81.8)	85.4 (80.0)		
Combined CIK cell therapy				
Yes	28.0 (26.4)	32.8 (30.7)	0.483	0.107
No	78.1 (73.6)	74.0 (69.3)		

Data are presented as n (%). The corresponding d values were calculated after logarithmic transformation to account for nonparametric distributions. d values <0.1 indicate negligible differences, values between 0.1 and 0.3 indicate small differences, values between 0.3 and 0.5 indicate moderate differences, and values >0.5 indicate large differences. IPTW, inverse probability of treatment weight; KPS, Karnofsky Performance Scale; SCC, squamous cell carcinoma; AC, adenocarcinoma; SCLC, small cell lung cancer; TNM, tumor-node-metastasis; IO, immuno-oncology; PD-1, programmed cell death-1; PD-L1, programmed cell death ligand 1; CIK, cytokine-induced killer.

Table 2 Multivariate analysis of PFS

Parameter	Control	Comparison	Estimation	P value	HR	95% CI
Concomitant H1 antihistamines	No	Yes	−0.81	<0.001	0.44	0.31–0.65
Concomitant H2 antihistamines	No	Yes	0.88	<0.001	2.44	1.67–3.57
Age	≤60	>60	−0.13	0.43	0.88	0.63–1.22
Sex	Female	Male	0.07	0.69	1.08	0.76–1.54
KPS score	≤80	>80	−0.49	0.006	0.61	0.43–0.87
Pathological pattern	SCLC	SCC	−0.01	0.96	0.99	0.59–1.66
		Other	0.44	0.68	1.56	0.18–13.3
		AC	−0.11	0.68	0.9	0.54–1.50
TNM stage	III	IV	0.71	0.006	2.04	1.22–3.33
History of radiotherapy	No	Yes	0.01	0.96	1.01	0.68–1.49
History of surgery	No	Yes	−0.47	0.03	0.63	0.40–0.97
Number of IO lines	≥3	1	0.09	0.72	1.09	0.67–1.47
		2	0.05	0.83	1.05	0.68–1.62
Type of IO drug	PD-1	PD-L1	0.29	0.36	1.33	0.72–2.47
Combined chemotherapy	No	Yes	−0.48	0.02	0.62	0.41–0.93
Combined radiotherapy	No	Yes	−1.25	0.008	0.29	0.11–0.72
Combined anti-vascular therapy	No	Yes	−0.01	0.94	0.98	0.63–1.54
Combined cell therapy	No	Yes	−0.03	0.89	0.97	0.62–1.52

PFS, progression-free survival; KPS, Karnofsky Performance Scale; TNM, tumor-node-metastasis; IO, immuno-oncology; SCLC, small cell lung cancer; PD-1, programmed cell death-1; SCC, squamous cell carcinoma; AC, adenocarcinoma; PD-L1, programmed cell death ligand 1; HR, hazard ratio; CI, confidence interval.

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Table 3 Multivariate analysis of OS

Parameter	Control	Comparison	Estimation	P value	HR	95% CI
Concomitant H1 antihistamines	No	Yes	−0.47	0.047	0.62	0.39–0.99
Concomitant H2 antihistamines	No	Yes	0.86	<0.001	2.38	1.49–3.70
Age	≤60	>60	0.07	0.76	1.06	0.70–1.64
Sex	Female	Male	0.06	0.80	1.05	0.67–1.67
KPS score	≤80	>80	−0.29	0.16	0.75	0.49–1.12
Pathological pattern	SCLC	SCC	−0.83	0.014	0.44	0.23–0.84
		Other	0.08	0.94	1.08	0.11–10.77
		AC	−1	0.002	0.37	0.20–0.69
TNM stage	III	IV	0.61	0.06	1.85	0.96–3.57
History of radiotherapy	No	Yes	−0.53	0.048	0.59	0.35–1.00
History of surgery	No	Yes	−0.04	0.88	0.96	0.57–1.61
Number of IO lines	≥3	1	−0.55	0.08	0.58	0.31–1.07
		2	−0.37	0.16	0.69	0.41–1.17
Type of IO drug	PD-1	PD-L1	−0.01	0.97	0.99	0.43–2.25
Combined chemotherapy	No	Yes	−0.37	0.13	0.69	0.42–1.12
Combined radiotherapy	No	Yes	−2.19	0.03	0.11	0.02–0.83
Combined anti-vascular therapy	No	Yes	−0.15	0.61	0.86	0.50–1.52
Combined cell therapy	No	Yes	0.11	0.70	1.11	0.64–1.92

OS, overall survival; KPS, Karnofsky Performance Scale; TNM, tumor-node-metastasis; IO, immuno-oncology; SCLC, small cell lung cancer; PD-1, programmed cell death-1; SCC, squamous cell carcinoma; AC, adenocarcinoma; PD-L1, programmed cell death ligand 1; HR, hazard ratio; CI, confidence interval.

Results

Baseline patient characteristics

Among the 211 patients screened, 109 patients who received H1 antihistamine while administering anti-PD-1/PD-L1 therapy were screened into the experimental group. The remaining 102 patients who did not receive H1 antihistamines were included in the control group. The analysis of baseline factors between groups based on the original data is presented in *Table 1*. There were differences in multiple baseline factors, so the analysis charts generated based on the original data were highly biased. After the PS-based IPTW treatment, most baseline factors in the baseline factor analysis had d values <0.1, and only two factors had values slightly greater than 0.1 (0.1063 and 0.1068). The analysis charts based on the IPTW-adjusted data were used to answer medical questions.

After PS-based IPTW treatment, the baseline patient characteristics were balanced between the two groups. There was no statistically significant difference in relevant variables such as age, sex, KPS score, pathological pattern, TNM stage, history of radiotherapy and surgery, number of IO lines, type of IO drug, or other combined therapies. The median follow-up duration was 36.3 (range, 1.0–97.0) months in the experimental group and 39.5 (range, 1.7–77.0) months in the control group. There was no statistical difference in the follow-up time between the two groups (P=0.50).

Efficacy

In the IPTW-adjusted population, PFS time was analyzed for the two groups; the median PFS (mPFS) of the experimental group was 12.7 months [95% confidence interval (CI): 6.3–18.0], while that of the control group was 4.3 months (95% CI: 4.0–5.7), indicating a statistical difference (P<0.001) (*Figure 2A*). The PFS was higher

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in the experimental group than in the control group; the rates of 6-, 12-, and 18-month PFS for the experimental group were 67.3%, 51.5%, and 32.6%, respectively, while that in the control group was 36.3%, 22.4%, and 11.2%, respectively (*Figure 2A*). In the IPTW-adjusted population, the experimental group showed prolonged PFS compared to the control group in most subgroups (*Figure 2B*).

After IPTW, the median OS (*Figure 3A*) of the experimental and control groups was 32.8 months (95% CI: 23.2–NA) and 18.1 months (95% CI: 10.5–27.7), respectively, representing a significant difference (P=0.01). Meanwhile, a difference in the 1-, 2-, and 3-year OS was observed between the experimental (75.0%, 63.9%, and 40.1%, respectively) and control group (60.4%, 41.6%, and 30.0%, respectively). Analysis of the OS revealed a survival benefit for the experimental group in most subgroup populations (*Figure 3B*). The weighted single-factor analysis of PFS (HR 0.46, 95% CI: 0.35–0.63; P<0.001) and OS (HR 0.63, 95% CI: 0.44–0.91; P=0.01) indicated that concomitant administration H1 antihistamine was a favorable predictor, especially of PFS.

Multivariate Cox proportional hazard models were used to evaluate the effects of all potential prognostic factors on progression and survival measures. The results showed that the favorable predictors of PFS (*Table 2*) were concomitant H1 antihistamine use (HR 0.44, 95% CI: 0.31–0.65; P<0.001), KPS score >80 (HR 0.61, 95% CI: 0.43–0.87; P=0.006), combined chemotherapy (HR 0.62, 95% CI: 0.41–0.93; P=0.02), and radiotherapy (HR 0.29, 95% CI: 0.11–0.72; P=0.008). Meanwhile, the unfavorable predictors of PFS were concomitant use of the H2 antihistamine cimetidine (HR 2.44, 95% CI: 1.67–3.57; P<0.001) and TNM stage IV (HR 2.04, 95% CI: 1.22–3.33; P=0.006).

Moreover, favorable OS was associated with concomitant administration of H1 antihistamines (HR 0.62, 95% CI: 0.39–0.99; P=0.047) and radiotherapy (HR 0.11, 95% CI: 0.02–0.83; P=0.03) (*Table 3*). Patients who underwent therapy with H2 antihistamines combined with immune checkpoint blockade therapy had a 2.38-fold higher risk of mortality compared to those not receiving concurrent H2 antihistamines.

Primary outcomes in the subgroups

Further subgroup analyses were conducted (*Figure 4*). Analysis of PFS (*Figure 4A*) indicated that, in the experimental group, patients treated with only H1 antihistamine (n=40) had a longer PFS compared to those who received H1 plus H2 antihistamines (n=69) after IPTW (18.0 *vs.* 6.8 months; HR 0.40, 95% CI: 0.26–0.63; P<0.001). In the control group, patients who received no antihistamine (n=75) had a longer PFS than those who received only H2 antihistamines (n=27) after IPTW (5.8 *vs.* 4.1 months; HR 0.44, 95% CI: 0.29–0.67; P<0.001). Analysis of OS (*Figure 4B*) revealed that, in the experimental group, patients treated with only H1 antihistamine had a longer OS than those who received H1 plus H2 antihistamines after IPTW (not reached *vs.* 26.6 months; HR 0.55, 95% CI: 0.32–0.94, P=0.03). In the control group, patients who received no antihistamines had a longer OS than those who received only H2 antihistamines after IPTW (25.2 *vs.* 16.9 months; HR 0.61, 95% CI: 0.37–1.00, P=0.049). These results showed that H1 antihistamine may improve the efficacy of ICI immunotherapy, whereas H2 antihistamine could potentially diminish its effectiveness.

Safety

In the IPTW-adjusted population (*Table 4*), the rate of any grade of irAEs in the experimental group was 52.4% while that in the control group was 69.2% (P=0.01). The incidence of Grades ≥3 irAE was 4.5% in the experimental group and 25.9% in the control group (P<0.001). Meanwhile, the concomitant use of H1 antihistamine improved the safety profile for most of the recorded irAEs, although the difference was not statistically significant.

Discussion

We examined the effects of concomitant use of H1 antihistamines in patients receiving anti-PD-1/PD-L1 antibodies based on real-world data from a cohort of 211 patients. Patients with concomitant use of H1 antihistamines received better survival benefits and prolonged PFS compared to those in the control group before and after IPTW. The concomitant use of H2 antihistamines was associated with a lower OS and PFS in the subgroups.

Additionally, the mPFS and mOS were higher in the experimental group than in the control group. Concomitant H1 antihistamine use was identified as a favorable predictor, especially of PFS. These data suggest that H1 antihistamines augment T-cell-mediated antitumor immunity. Our subgroup analysis revealed that H2 antihistamines were associated with poorer efficacy, a conclusion not corroborated by recent experimental

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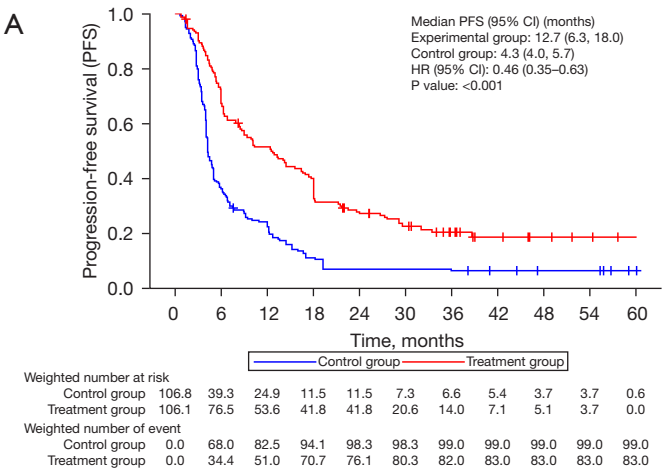

B

Subgroup	All	Weighted Experimental group	Weighted Control group	Hazard ratio 95% CI	HR (95% CI)
Age (years)					
≤60	89.2	42.9	46.3		0.48 (0.30 to 0.77)
>60	123.7	63.2	60.5		0.47 (0.32 to 0.69)
Gender					
Male	158.4	76.5	81.9		0.41 (0.29 to 0.58)
Female	54.5	29.6	24.8		0.68 (0.38 to 1.22)
KPS score (range)					
≤80	140.5	71.3	69.2		0.39 (0.27 to 0.56)
>80	72.4	34.8	37.5		0.51 (0.30 to 0.89)
Pathological pattern					
Squamous cell carcinoma	83.5	41.1	42.5		0.60 (0.38 to 0.97)
Adenocarcinoma	98.7	50.0	48.7		0.32 (0.20 to 0.51)
Small cell carcinoma	28.8	14.1	14.7		0.71 (0.33 to 1.54)
TNM stage					
III	25.5	14.0	11.4		0.97 (0.40 to 2.34)
IV	187.4	92.1	95.3		0.41 (0.30 to 0.57)
History of radiotherapy					
Yes	40.1	18.9	21.3		0.85 (0.42 to 1.69)
No	172.7	87.2	85.5		0.40 (0.28 to 0.55)
History of surgery					
Yes	28.4	14.0	14.4		0.35 (0.14 to 0.90)
No	184.5	92.2	92.3		0.48 (0.35 to 0.66)
Number of IO lines					
1	103.1	52.7	50.4		0.43 (0.28 to 0.64)
2	68.7	33.5	35.2		0.52 (0.31 to 0.90)
≥3	41.1	19.9	21.2		0.49 (0.24 to 1.03)
Type of IO drug					
PD-1	198.8	98.9	100.0		0.44 (0.32 to 0.60)
PD-L1	14.1	7.3	6.8		0.66 (0.21 to 2.10)
Combined cimetidine					
Yes	102.1	51.3	50.8		0.45 (0.29 to 0.70)
No	110.8	54.8	56.0		0.42 (0.27 to 0.65)
Combined chemotherapy					
Yes	145.3	71.7	73.6		0.39 (0.27 to 0.56)
No	67.6	34.4	33.1		0.64 (0.38 to 1.07)
Combined radiotherapy					
Yes	5.8	3.4	2.4		0.88 (0.12 to 6.66)
No	207.1	102.7	104.4		0.46 (0.34 to 0.62)
Combined antivascular therapy					
Yes	40.7	19.3	21.4		0.21 (0.09 to 0.49)
No	172.2	86.8	85.4		0.55 (0.40 to 0.76)
Combined cell therapy					
Yes	60.8	28.0	32.8		0.25 (0.13 to 0.48)
No	152.1	78.1	74.0		0.56 (0.39 to 0.79)

Figure 2 Kaplan-Meier plots for PFS and forest plots of weighted PFS in the experimental and control groups after IPTW adjustment. (A) PFS. (B) Forest plot of weighted PFS. PFS, progression-free survival; CI, confidence interval; KPS, Karnofsky Performance Scale; TNM, tumor-node-metastasis; IO, immuno-oncology; PD-1, programmed cell death-1; PD-L1, programmed cell death ligand 1; HR, hazard ratio; IPTW, inverse probability of treatment weight.

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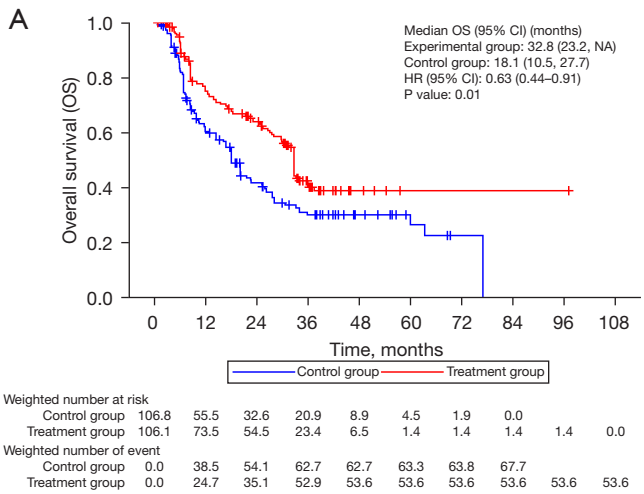

B

Subgroup	All	Weighted Experimental group	Weighted Control group	Hazard ratio 95% CI	HR (95% CI)
Age (years)					
≤60	89.2	42.9	46.3		0.68 (0.38 to 1.22)
>60	123.7	63.2	60.5		0.61 (0.38 to 0.97)
Gender					
Male	158.4	76.5	81.9		0.52 (0.34 to 0.79)
Female	54.5	29.6	24.8		1.29 (0.61 to 2.72)
KPS score (range)					
≤80	140.5	71.3	69.2		0.77 (0.49 to 1.21)
>80	72.4	34.8	37.5		0.44 (0.23 to 0.86)
Pathological pattern					
Squamous cell carcinoma	83.5	41.1	42.5		0.77 (0.43 to 1.37)
Adenocarcinoma	98.7	50.0	48.7		0.53 (0.30 to 0.92)
Small cell carcinoma	28.8	14.1	14.7		0.78 (0.32 to 1.93)
TNM stage					
III	25.5	14.0	11.4		0.83 (0.27 to 2.61)
IV	187.4	92.1	95.3		0.63 (0.43 to 0.92)
History of radiotherapy					
Yes	40.1	18.9	21.3		0.60 (0.24 to 1.50)
No	172.7	87.2	85.5		0.62 (0.41 to 0.92)
History of surgery					
Yes	28.4	14.0	14.4		0.39 (0.14 to 1.14)
No	184.5	92.2	92.3		0.68 (0.46 to 1.01)
Number of IO lines					
1	103.1	52.7	50.4		0.55 (0.33 to 0.93)
2	68.7	33.5	35.2		0.88 (0.45 to 1.74)
≥3	41.1	19.9	21.2		0.48 (0.21 to 1.14)
Type of IO drug					
PD-1	198.8	98.9	100.0		0.60 (0.41 to 0.87)
PD-L1	14.1	7.3	6.8		1.01 (0.20 to 4.97)
Combined cimetidine					
Yes	102.1	51.3	50.8		0.66 (0.39 to 1.09)
No	110.8	54.8	56.0		0.58 (0.35 to 0.98)
Combined chemotherapy					
Yes	145.3	71.7	73.6		0.50 (0.31 to 0.80)
No	67.6	34.4	33.1		0.92 (0.51 to 1.65)
Combined radiotherapy					
Yes	5.8	3.4	2.4		>999 (0.00 to –)
No	207.1	102.7	104.4		0.62 (0.43 to 0.89)
Combined antivascular therapy					
Yes	40.7	19.3	21.4		0.44 (0.16 to 1.22)
No	172.2	86.8	85.4		0.67 (0.45 to 0.99)
Combined cell therapy					
Yes	60.8	28.0	32.8		0.21 (0.10 to 0.45)
No	152.1	78.1	74.0		0.98 (0.63 to 1.51)

Figure 3 Kaplan-Meier plots for OS and forest plot of weighted OS in the experimental and control groups after IPTW adjustment. (A) OS. (B) Forest plot of weighted OS. OS, overall survival; CI, confidence interval; NA, not available; KPS, Karnofsky Performance Scale; TNM, tumor-node-metastasis; IO, immuno-oncology; PD-1, programmed cell death-1; PD-L1, programmed cell death ligand 1; HR, hazard ratio; IPTW, inverse probability of treatment weight.

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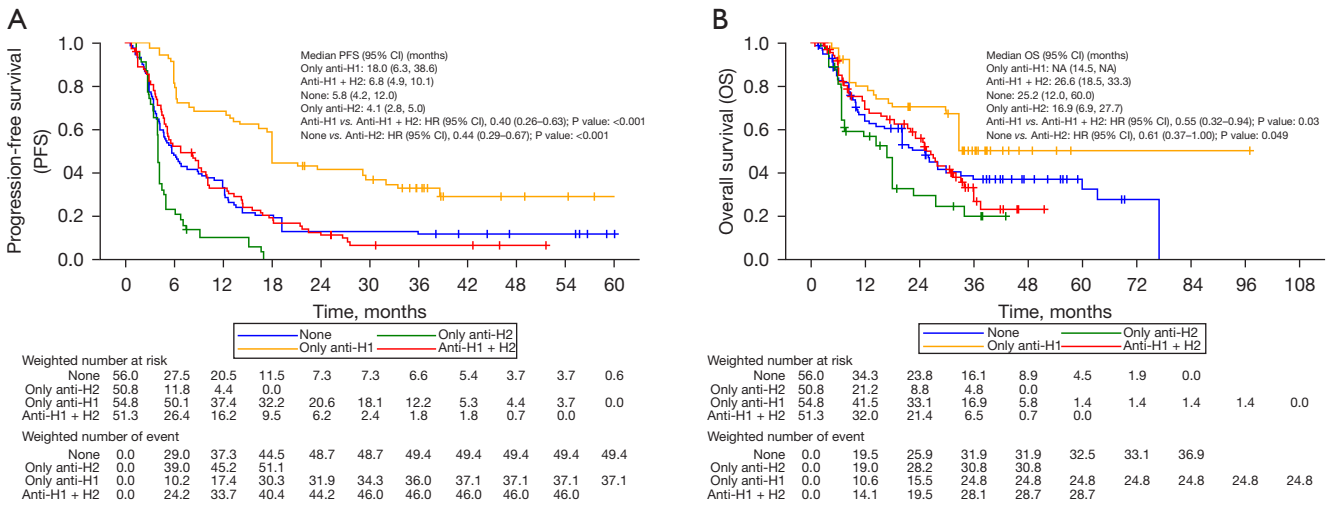

Figure 4 Kaplan-Meier plots for the subgroup analysis for PFS and OS according to concomitant use of H2 antihistamines after IPTW adjustment. (A) PFS. (B) OS. PFS, progression-free survival; OS, overall survival; CI, confidence interval; HR, hazard ratio; NA, not available; IPTW, inverse probability of treatment weight.

data but mentioned in some retrospective clinical analyses (12,13). H2 antihistamines may diminish the effectiveness of other anticancer medications through their influence on gut microbiota (12,13).

The role of histamine and histamine receptors in cancer development remains controversial. Low histamine concentrations promote the proliferation of prostate cancer cells, while high histamine concentrations can inhibit the proliferation of prostate cancer cells (14). Similar findings have been observed in breast and pancreatic cancer cell lines (15,16). Studies have revealed that histamine is often present in high concentrations in the plasma and tumor tissues of patients with cancer (17,18). In an *in vivo* study using a melanoma xenograft model (19) and an *in vitro* study using mouse spleen cells (20), histamine was found to promote cancer progression by inducing cell proliferation and activating the regulatory T cells responsible for immune suppression. In contrast, cancer cells frequently upregulate the histamine-synthesizing enzyme L-histidine decarboxylase, leading to increased histamine levels in patients with cancer (21,22). Histamine receptors are highly expressed in various malignant tumor tissues, such as those of the breast, bowel, pancreas, and prostate. They are positively correlated with the clinical stage of the tumor and negatively correlated with patient prognosis (23,24).

The histamine receptors H1R and H2R exert proangiogenic effects and can promote tumor growth by regulating metabolic pathways when bound to histamine (25,26). Histamine promotes tumor cell proliferation through H1R and suppresses the immune response through H2R by reversing the inhibition of natural killer cells by macrophages (27).

The effect of antihistamines on tumors varies according to tumor type, antihistamine type, route, and administration dosage. Several *in vitro* cell experiments have demonstrated that antihistamines can inhibit the reproduction of tumor cells by inducing apoptosis (21,28), and some animal experiments have shown that antihistamines can inhibit tumor growth and prolong the survival rate of tumor-bearing mice (28,29). Concurrent animal experiments demonstrated that antihistamines inhibited tumor growth and prolonged survival in mice with B16F10 melanoma (29).

Regarding safety, the results of our study indicate that the use of H1 antihistamines may reduce the incidence of irAEs and provide a better safety profile for most recorded irAEs. Our retrospective analysis also revealed a significant reduction in serious AEs (grade ≥3) in patients with concomitant antihistamine use. The control group was more likely to develop severe immune-related pneumonia or heart damage events that were grade ≥3 or even fatal, although statistical significance was not observed. Using H1 antihistamines can reduce the number of multisystem irAEs in individual patients, which may be related to its inhibition of mast cell destruction of normal tissues (30).

The incidence of skin toxicity was lower in the control group than in the concomitant antihistamine group, which

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Table 4 Occurrence of irAEs in the two groups in the IPTW-adjusted population

irAE	Experimental group (n=106.1)	Control group (n=106.8)	P value*	RR (95% CI)
Any irAE	55.6 (52.4)	73.9 (69.2)	0.01	0.76 (0.61, 0.95)
≥G3	4.8 (4.5)	27.7 (25.9)	<0.001	0.17 (0.07, 0.44)
Skin damage	12.4 (11.7)	11.2 (10.5)	0.76	1.12 (0.52, 2.41)
≥G3	0.6 (0.5)	3.0 (2.8)	0.25	0.19 (0.01, 3.26)
Abnormal thyroid function	33.9 (31.9)	50.5 (47.3)	0.02	0.67 (0.48, 0.95)
≥G3	1.6 (1.5)	0.5 (0.5)	0.48	2.95 (0.14, 63.62)
Hyperthyroidism	6.2 (5.8)	12.6 (11.8)	0.13	0.49 (0.19, 1.24)
≥G3	0.0 (0.0)	0.5 (0.5)	0.97	0.00 (0.00, >99.99)
Hypothyroidism	32.4 (30.5)	46.4 (43.4)	0.056	0.70 (0.49, 1.01)
≥G3	1.6 (1.5)	0.5 (0.5)	0.48	2.95 (0.14, 63.62)
Cortisol reduced	18.0 (17.0)	11.7 (11.0)	0.21	1.54 (0.78, 3.07)
≥G3	0.0 (0.0)	1.9 (1.8)	0.97	0.00 (0.00, >99.99)
Abnormal blood sugar	5.2 (4.9)	16.4 (15.3)	0.02	0.32 (0.12, 0.83)
≥G3	0.0 (0.0)	13.2 (12.3)	0.96	0.00 (0.00, >99.99)
Pneumonia	0.0 (0.0)	0.6 (0.6)	0.97	0.00 (0.00, >99.99)
≥G3	0.0 (0.0)	0.6 (0.6)	0.97	0.00 (0.00, >99.99)
Myositis	6.7 (6.3)	13.8 (13.0)	0.11	0.49 (0.20, 1.19)
≥G3	0.7 (0.6)	6.7 (6.3)	0.07	0.10 (0.01, 1.23)
Heart damage	13.0 (12.2)	28.3 (26.5)	0.01	0.46 (0.25, 0.84)
≥G3	1.2 (1.2)	2.3 (2.1)	0.59	0.55 (0.06, 4.90)
Liver damage	4.0 (3.8)	8.0 (7.5)	0.25	0.50 (0.16, 1.63)
≥G3	0.0 (0.0)	0.0 (0.0)	1.00	1.00 (0.00, >99.99)
Kidney damage	2.2 (2.1)	0.6 (0.5)	0.36	3.88 (0.21, 72.64)
≥G3	0.0 (0.0)	0.6 (0.5)	0.97	0.00 (0.00, >99.99)
Gastrointestinal	3.4 (3.2)	9.9 (9.3)	0.08	0.34 (0.10, 1.15)
≥G3	0.7 (0.6)	1.2 (1.2)	0.67	0.53 (0.03, 10.69)

*, P values derived from logistic regression. The experimental group had immune toxicities of any grade in 52.4% of patients and grade 3–5 toxicities in 4.5%. The control group showed immune toxicities of any grade in 69.2% of patients and grade 3–5 toxicities in 25.9%. irAE, immune-related adverse event; IPTW, inverse probability of treatment weight; G, grade; RR, relative risk; CI, confidence interval.

may be attributable to the early attention to the rash and lack of documentation. Endocrine toxicity is the most common form of thyrotoxicity, which often manifests as hypothyroidism. Laboratory test results suggest (31) that thyrotoxicity often manifests as a transient hyperthyroid phase, followed by a prolonged hypothyroidism phase, which often requires long-term exogenous thyroid hormone therapy. Pituitary inflammation often presents as a low cortisol level, which may be difficult to correct and also necessitates long-term hormone replacement therapy, depending on symptom severity.

Antihistamines have been proven to be safe, reliable, and inexpensive long-term clinical drugs. They are more effective when combined with antineoplastic drugs. However, evidence is limited to cells and animal experiments, and with clinical research being relatively

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sparse, further supplementation and development are needed. Based on our data, we believe that low-cost H1 antihistamines can be used in combination with immunotherapy as an adjuvant therapy to more effectively treat patients with cancer.

This study had some limitations which should be addressed. First, our real-world study involved only a single center, the number of patients was limited, and biases from geographic to demographic characteristics were unavoidable. Even though we used IPTW analysis to balance the two groups, a retrospective analysis of real-world data cannot provide the same level of evidence as a randomized controlled trial. However, the applied statistical design reduced potential confounders. Second, other drugs may potentially exert effects, and our analysis, unlike a randomized trial, could not account for unmeasured confounding factors. Nonetheless, our findings can serve as useful and reliable information for clinicians and potentially benefit patients. Currently, we have initiated a prospective clinical study of first-line Tislelizumab combined with standard chemotherapy, with or without H1 antihistamines, in advanced non-small cell lung cancer, hoping to verify the outcomes of the retrospective study in the future.

Conclusions

Patients treated with concomitant H1 antihistamines had a better survival benefit and prolonged PFS than those in the control group before and after IPTW. In contrast, the concomitant use of H2 antihistamines was associated with a lower OS and PFS in the subgroups. Additionally, our findings indicate that concomitant use of H1 antihistamines can provide a better safety profile for most recorded irAEs. These results support the potential utility of low-cost H1 antihistamines as an adjuvant therapy combined with immunotherapy to treat cancer patients more effectively.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-795/rc

Data Sharing Statement: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-795/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-795/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All patients signed an informed consent form before immunotherapy and agreed to their data being used for the study. This study was conducted in compliance with the ethical principles of the Declaration of Helsinki (as revised in 2013) and was approved by the review board of the Ethics Committee of Tianjin Medical University Cancer Institute and Hospital (No. E20241045).

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