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Efficacy and safety of H1 receptor antagonists combined with PD-1 inhibitors and chemotherapy in advanced lung squamous cell carcinoma

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Abstract: Objective To investigate the efficacy and safety of H1 receptor antagonists (H1RAs) combined with programmed death protein 1 (PD-1) inhibitor and chemotherapy for advanced lung squamous cell carcinoma (LSCC), so as to provide a reference for the clinical treatment of LSCC. **Methods** A total of 139 patients with stage Ⅲ-Ⅳ LSCC in the First Affiliated Hospital with Nanjing Medical University from January 2020 to September 2022 were retrospectively enrolled. Sixty-nine patients in the treatment group received H1RAs combined with PD-1 inhibitors and chemotherapy, while 70 patients in the control group were treated with PD-1 inhibitors plus chemotherapy. All patients were followed up until June 30, 2025. The overall survival (OS) of the two groups was analyzed, along with progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR)in the first-line treatment subgroup, and the safety profile of the total population. **Results** There was no statistically significant difference in baseline data between the two groups (P>0.05). Each group had 60 cases as first-line treatment. The median OS in the treatment group was significantly longer than that in the control group (19.7 months *vs* 16.3 months, P=0.018). The median PFS in the first-line treatment subgroup of the treatment group was also superior to that of the first-line subgroup of the control group (9.4 months *vs* 7.1 months, P<0.01). No statistically significant difference was observed in ORR (63.3% *vs* 55.0%, χ^2 =0.862, P=0.353) and DCR (91.7% *vs* 88.3%, χ^2 =1.294, P=0.255) between the first-line subgroup of treatment group and the first-line subgroup of control group. The incidence rates of treatment-related adverseevents (TRAEs) of any grade and grade ⩾3 TRAEs showed no statistically significant difference between the two groups (P>0.05). **Conclusion** The addition of H1RAs to PD-1 inhibitor plus chemotherapy regimen may bring better survival benefits to patients with advanced LSCC without increasing the overall incidence of adverse reactions.

Keywords: H1 receptor antagonists; Programmed cell death protein 1 inhibitor; Lung squamous cell carcinoma; Immunotherapy; Chemotherapy; Overall survival

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Lung squamous cell carcinoma (LSCC) is an important subtype of non-small cell lung cancer. For patients with unresectable locally advanced or metastatic disease, programmed death protein 1 (PD-1) inhibitors combined with chemotherapy have become the standard first-line treatment regimen[1-3], which significantly improves the overall survival (OS) of patients. However, a large number of patients still develop drug resistance, so exploring strategies to enhance the efficacy of PD-1 inhibitors is a current research hotspot. Recent studies have found that macrophages, dendritic cells and histamine in the tumor microenvironment play key roles in immune regulation. Histamine binds to H1 receptors on immune cells, promoting the polarization of macrophages into an M2-like immunosuppressive phenotype[4]. It inhibits the maturation and antigen presentation function of dendritic cells, and promotes the aggregation of myeloid-derived suppressor cells, thereby establishing an immunosuppressive microenvironment [5-7]. Preclinical studies have confirmed that H1 receptor antagonists (H1RAs) can reverse this immunosuppression and enhance the anti-tumor effect of PD-1 inhibitor therapy[8-10]. Recently, multiple retrospective analyses in solid tumors of multiple tumor types have shown that concurrent use of H1RAs during PD-1 inhibitor treatment is associated with a positive trend of improvement in patients' OS and progression-free survival (PFS) [11-13]. This study conducts a retrospective cohort analysis to evaluate the efficacy and safety of H1RAs combined with PD-1 inhibitors and chemotherapy in the treatment of advanced LSCC.

1 Materials and Methods

1.1 Clinical Data

This study was a single-center, retrospective cohort study that included the clinical data of 139 patients with pathologically confirmed stage III-IV unresectable LSCC admitted to the First Affiliated Hospital of Nanjing Medical University from January 2020 to September 2022.

Inclusion criteria: (1) Aged 18-80 years; (2) Eastern Cooperative Oncology Group (ECOG) performance status score of 0-2; (3) Histologically confirmed LSCC; (4) Radiologically confirmed stage

III-IV, unresectable; (5) Normal organ function; (6) Received at least 4 cycles of PD-1 inhibitor combined with chemotherapy; (7) Complete clinical data and follow-up records available.

Exclusion criteria: (1) Concomitant with other active malignant tumors; (2) Concomitant with unstable brain or meningeal metastasis.

Patients were divided into the treatment group and the control group according to the treatment regimen. The treatment group received the regimen of H1RAs + PD-1 inhibitor + chemotherapy, specifically: during PD-1 inhibitor combined with chemotherapy, patients regularly took H1RAs for any reason (such as allergy, rash, pruritus) with a medication duration ≥ 3 months. The control group only received the regimen of PD-1 inhibitor + chemotherapy, specifically: patients who did not use any H1RAs during PD-1 inhibitor combined with chemotherapy. All patients and their families signed informed consent for the treatment regimen. This study was approved by the Ethics Committee of the First Affiliated Hospital of Nanjing Medical University (Ethics No.: 2025-SR-794).

1.2 Research Methods

Patient data (name, gender, age, pathological diagnosis, stage, ECOG score, etc.), treatment regimens, concomitant medication of glucocorticoids and antibiotics, efficacy evaluation, and adverse event data were collected from the electronic medical record system. The PD-1 inhibitors mainly included camrelizumab, tislelizumab, or sintilimab, all administered at a fixed dose of 200 mg every 3-4 weeks (q3-4w). For first-line chemotherapy regimens, the main agents were paclitaxel liposome (135-175 mg/m²), albumin-bound paclitaxel (260 mg/m²), or paclitaxel polymer micelle (230-300 mg/m²) combined with carboplatin (AUC=5) or nedaplatin (80-100 mg/m²), q3-4w. For second-line and later-line regimens, the main agents were gemcitabine (1 000 mg/m² on days 1 and 8) or docetaxel (60-75 mg/m²), q3-4w. Single-dose glucocorticoids used in routine clinical antiemetic preconditioning regimens were not included in the statistics.

1.3 Follow-up

The main follow-up method of this study was active monitoring through the hospital electronic medical record system, supplemented by telephone follow-up. The follow-up cutoff date was June 30, 2025. For patients who did not experience endpoint events (disease progression or death) before the cutoff date, their survival time was treated as censored data, and the last contact date was taken as the follow-up endpoint.

1.4 Therapeutic Efficacy Assessment

Tumor efficacy was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. All patients completed imaging evaluation (enhanced computed tomography of the chest, abdomen, and pelvis) before treatment (baseline), and efficacy assessment was performed every 2 treatment cycles, until confirmed disease progression, death, or the study cutoff date. Efficacy was classified as follows. Complete response (CR): disappearance of all target and non-target lesions, with no new lesions observed. Partial response (PR): reduction in the sum of diameters of target lesions ≥30% compared with baseline. Progressive disease (PD): increase in the sum of diameters of target lesions ≥20% compared with the smallest recorded value, or occurrence of one or more new lesions, or definite progression of non-target lesions. Stable disease (SD): target lesion shrinkage did not meet the PR criteria, or enlargement did not meet the PD criteria.

The primary endpoint was overall survival (OS), defined as the time from the date of treatment initiation to death from any cause. Secondary endpoints included the following: (1) PFS in first-line treatment patients, defined as the time from initiation of first-line treatment to disease progression or death from any cause; (2) Objective response rate (ORR) in first-line treatment patients, defined as the proportion of patients who achieved CR or PR in the total study population; (3) Disease control rate (DCR), defined as the proportion of patients who achieved CR, PR, or SD.

Safety data included treatment-related adverse events (TRAEs) and immune-related adverse events (irAEs), which were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

1.5 Statistical Methods

Data were analyzed using SPSS 22.0 software, and graphs were plotted using GraphPad Prism 10.6 software. Categorical variables were presented as n (%), and intergroup comparisons were performed using the χ^2 test or Fisher's exact test. Continuous variables conforming to normal distribution were presented as $\bar{x}\pm s$, and intergroup comparisons were performed using the independent samples t test. Survival analysis was conducted using the Kaplan-Meier method and log-rank test. The Cox proportional hazards regression model was used to calculate the hazard ratio (HR). A P value < 0.05 was considered statistically significant.

2 Results

2.1 Baseline Characteristics of Patients

A total of 139 patients were included in the analysis, with 69 patients in the treatment group. The H1RAs administered included cetirizine (9 cases), loratadine (45 cases), desloratadine (10 cases), and desloratadine citrate disodium (5 cases). The control group included 70 patients. There were no statistically significant differences between the two groups in terms of age,

gender, ECOG performance status score, treatment line, tumor stage, proportion of brain/liver metastasis, PD-L1 Tumor Cell Proportion Score (TPS), proportion of patients receiving combined radiotherapy, and concurrent medications (glucocorticoids or antibiotics) (P > 0.05). **[Table 1]**

Tab.1 Comparison of baseline characteristics between the two groups [case (%)]

Item	Treatment group (n=69)	Control group (n=70)	t/χ^2 value	P value
Age (years, $\bar{x}\pm s$)	66.6±9.4	67.1±7.7	0.338	0.736
Gender				
Male	61（88.4）	60（85.7）	0.223	0.637
Female	8（11.6）	10（14.3）		
ECOG performance status score				
0–1 point	56（81.2）	57（81.4）	0.002	0.968
2 point	13（18.8）	13（18.6）		
Treatment line				
1	60（87.0）	60（85.7）		
2	5（7.2）	6（8.6）	0.084	0.959
≥3	4（5.8）	4（5.7）		
Tumor stage				
Stage III	32（46.4）	32（45.7）	0.006	0.938
Stage IV	37（53.6）	38（54.3）		
Brain metastasis	6（8.7）	7（10.0）	0.700	0.792
Liver metastasis	22（31.9）	25（35.7）	0.228	0.633
PD-L1 TPS				
<1%	6（8.7）	5（7.1）		
≥1%	22（31.9）	20（28.6）	0.365	0.833
Unknown	41（59.4）	45（64.3）		
Combined radiotherapy				
Yes	8（11.6）	10（14.3）	0.223	0.637
No	61（88.4）	60（85.7）		
Concurrent glucocorticoid use[a]				
Yes	8（11.6）	10（14.3）	0.223	0.637
No	61（88.4）	60（85.7）		
Concurrent antibiotic use				
Yes	7（10.1）	6（8.6）	0.101	0.750
No	62（89.9）	64（91.4）		

Note: [a] indicates that single-use glucocorticoids in routine clinical antiemetic preconditioning regimens are excluded from statistical analysis.

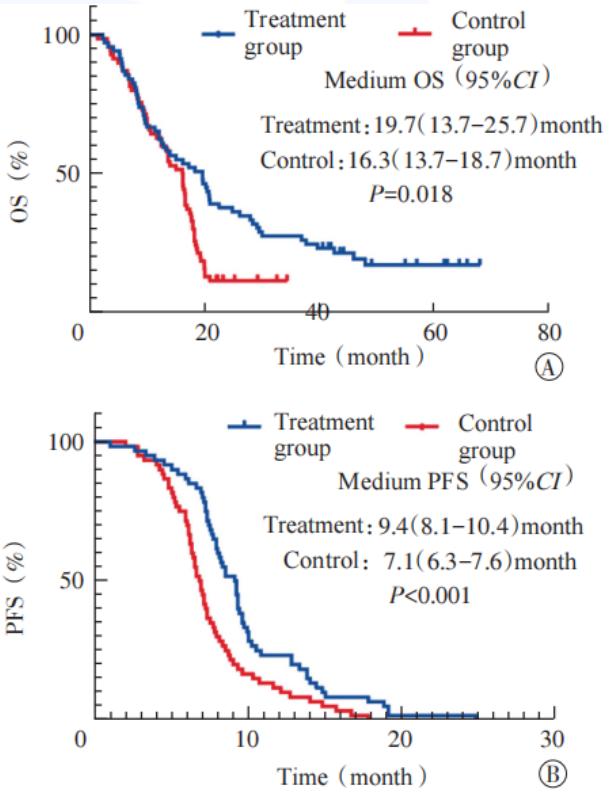
2.2 Efficacy Outcomes

The median follow-up duration was 36.5 months. The median OS of the treatment group was 19.7 months (95%*CI*: 13.7–25.7), which was significantly longer than 16.3 months (95%*CI*: 13.7–18.7) in the control group (*HR* = 0.56, 95%*CI*: 0.38–0.83, P = 0.018), as shown in **Figure 1A**. A total of 120 patients received first-line treatment, including 60 in the treatment group and 60 in the control group. The median progression-free survival (PFS) of the treatment group was 9.4 months (95%*CI*: 8.1–10.4), which was superior to 7.1 months (95%*CI*: 6.3–7.6) in the control group (*HR* = 0.53, 95%*CI*: 0.36–0.76, P < 0.01), as shown in **Figure 1B**. There were no statistically significant differences in objective response rate (ORR) (63.3% *vs* 55.0%, P = 0.353) and disease control rate (DCR) (91.7% *vs* 88.3%, P = 0.255) between the first-line subgroup of the treatment group and the first-line subgroup of the control group. **[Table 2]**

2.3 Analysis of safety

The TRAEs of the two groups are shown in **Table 3**. There were no statistically significant differences in the incidence of any-grade TRAEs and grade ≥ 3 TRAEs between the two groups (P>0.05). Hematological toxicities (neutropenia, thrombocytopenia, anemia) and fatigue were the most common adverse events in both groups, with comparable incidence rates between groups.

In terms of irAEs, the overall incidence of any-grade irAEs was similar between the two groups (60.9% *vs* 65.7%, P=0.553). The incidence of any-grade pruritus (26.1% *vs* 1.4%, P<0.01) and rash (17.4% *vs* 2.9%, P=0.004) in the treatment group was significantly higher than that in the control group. There were no statistically significant differences in the incidence of other common irAEs, including elevated aspartate aminotransferase (AST)/alanine aminotransferase (ALT), thyroid dysfunction, and pneumonitis, between the two groups (P>0.05). The incidence of grade ≥ 3 irAEs and permanent discontinuation of immunotherapy due to irAEs showed no significant difference between the treatment group and the control group (11.6% *vs* 21.4%, P=0.119; 5.8% *vs* 8.6%, P=0.745).



Note: A, OS curves of the treatment group and the control group; B, PFS curves of the first-line treatment subgroups of the two groups.

Fig.1 Survival curves of the two groups of patients

Tab.2 Tumor treatment response in first-line therapy subgroups [*n*=60, case (%)]

Groups	CR	PR	SD	PD	ORR(%)	DCR(%)
First-line subgroup of the treatment group	0	38（63.3）	17（28.3）	5（8.3）	38（63.3）	55（91.7）
First-line subgroup of the control group	0	33（55.0）	20（33.3）	7（11.7）	33（55.0）	51（88.3）
χ^2 value					0.862	1.294
P value					0.353	0.255

Tab.3 Treatment-related adverse events [case (%)]

Adverse event	Treatment group (*n*=69)	Control group (*n*=70)	χ^2 value	*P* value
Any-grade TRAEs	65（94.2）	68（97.1）		0.441[a]
Neutropenia	25（36.2）	28（40.0）	0.209	0.647
Anemia	18（26.1）	20（28.6）	0.108	0.742
Thrombocytopenia	12（17.4）	15（21.4）	0.362	0.547
Fatigue	10（14.5）	13（18.6）	0.419	0.518
Grade ≥ 3 TRAEs	38（55.1）	42（60.0）	0.345	0.557
Any-grade irAEs	42（60.9）	46（65.7）	0.351	0.553
Pruritus	18（26.1）	1（1.4）	17.904	＜0.001
Rash	12（17.4）	2（2.9）	8.104	0.004
Elevated ALT	8（11.6）	10（14.3）	0.223	0.637
Elevated AST	7（10.1）	10（14.3）	0.555	0.456
Thyroid dysfunction	7（10.1）	9（12.9）	0.251	0.616
Pneumonitis	3（4.3）	6（8.6）		0.493[a]
Grade ≥ 3 irAEs	8（11.6）	15（21.4）	2.434	0.119
Discontinuation due to irAEs	4（5.8）	6（8.6）		0.745[a]

Note: [a] indicated that Fisher's exact test was used.

3 Discussion

This study explored the effect of concurrent H1RAs on efficacy and safety in patients with advanced LSCC receiving PD-1 inhibitor plus chemotherapy via a retrospective cohort analysis. The results showed that compared with immunotherapy plus chemotherapy alone, patients receiving additional H1RAs achieved significant improvements in OS and PFS in the first-line treatment subgroup. There were no statistically significant differences in ORR and DCR between the two groups. Safety analysis indicated that the addition of H1RAs did not increase the risk of TRAEs.

In recent years, immune checkpoint inhibitor plus chemotherapy has become the standard first-line treatment regimen for advanced LSCC [1-3], yet a considerable proportion of patients still face primary or secondary drug resistance. Therefore, exploring strategies that can reverse the immunosuppressive tumor microenvironment and enhance the efficacy of immunotherapy is of important clinical significance. Previous basic research and clinical retrospective evidence have found that H1RAs may improve the tumor immune microenvironment by antagonizing the binding of histamine to H1 receptors, thereby enhancing the efficacy of PD-1 inhibitors. Histamine can inhibit the function of macrophages and dendritic cells via H1 receptors, and promote the aggregation of myeloid-derived suppressor cells, leading to an immunosuppressive state [4-6]. H1RAs may reverse this process and restore T cell-mediated anti-tumor immune responses. This mechanistic hypothesis is supported by clinical observations: recent retrospective analyses in multiple solid tumors have found that concurrent use of H1RAs during PD-1 inhibitor treatment is associated with an improving trend in patients' OS and PFS [14-16].

The results of this study further validate the above viewpoints. In the overall population, the median OS of the treatment group was 3.4 months longer than that of the control group (19.7 months *vs* 16.3 months), with a HR of 0.56, which was statistically significant. In the first-line treatment subgroup, the median PFS of the treatment group was also significantly superior to that of the control group (9.4 months *vs* 7.1 months). These clinical results are consistent with previous basic and retrospective research evidence, collectively supporting the view that H1RAs can enhance the efficacy of immunotherapy by antagonizing H1 receptors and improving the tumor immune microenvironment [17-19].

In terms of safety, there were no statistically significant differences in the incidence of any-grade and grade ≥ 3 TRAEs between the two groups, suggesting that the combination of H1RAs does not increase the overall toxicity burden of chemotherapy or PD-1 inhibitor treatment. It is worth noting that although the incidence of any-grade pruritus and rash in the treatment group was significantly higher than that in the control group, this may be related to the medication indication of H1RAs for managing allergic symptoms. The incidence of grade ≥ 3 irAEs was numerically lower in the treatment group than in the control group (11.6% *vs* 21.4%, $P = 0.119$). This observation deserves further attention, but its clinical significance and correlation with H1RAs need to be clarified in future studies.

The limitations of this study include its retrospective design, limited sample size, and potential confounding factors, which may affect the efficacy assessment. It should be noted that multiple H1RAs, such as cetirizine, loratadine, and desloratadine, were used in the treatment group of this study, with medication indications including allergy, rash and other causes. The lipophilicity, receptor selectivity and immunomodulatory activity of different

drugs may vary, and this heterogeneity may affect the consistency of efficacy. Due to the limited number of cases in each subgroup, this study did not perform subgroup analysis by specific drug type. Future studies should unify the drug type as much as possible to enhance the reliability of the conclusions. Despite these limitations, this study provides preliminary clinical evidence for "drug repurposing", supporting the potential value of H1RAs as sensitizers for PD-1 inhibitor therapy. It is necessary to conduct prospective randomized controlled trials in the future to further verify the sensitizing effect of H1RAs in PD-1 inhibitor plus chemotherapy for advanced LSCC.

Conflict of Interest None

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·肺癌专题·论著·

H1受体阻滞剂联合PD-1抑制剂和化疗治疗晚期肺鳞状细胞癌的疗效及安全性

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摘要：目的　探讨H1受体阻滞剂（H1RAs）联合程序性死亡受体-1（PD-1）抑制剂和化疗治疗晚期肺鳞状细胞癌（LSCC）的疗效及安全性，为LSCC的治疗提供参考。**方法**　回顾性纳入2020年1月至2022年9月南京医科大学第一附属医院收治的139例Ⅲ~Ⅳ期LSCC患者。治疗组69例接受H1RAs联合PD-1抑制剂和化疗，对照组70例仅接受PD-1抑制剂和化疗。随访至2025年6月30日，分析两组总生存期（OS）以及一线亚组无进展生存期（PFS）、客观缓解率（ORR）、疾病控制率（DCR）和总人群的安全性。**结果**　两组基线资料比较差异无统计学意义（P>0.05）。每组各有60例为一线治疗。治疗组中位OS较对照组延长（19.7个月 *vs* 16.3个月，P=0.018），治疗组一线亚组的中位PFS也优于对照组一线亚组（9.4个月 *vs* 7.1个月，P<0.01）。治疗组一线亚组和对照组一线亚组ORR（63.3% *vs* 55.0%，χ^2=0.862，P = 0.353）和DCR（91.7% *vs* 88.3%，χ^2=1.294，P=0.255）比较差异无统计学意义。任何级别的治疗相关不良事件（TRAEs）以及≥3级TRAEs的发生率在两组间差异无统计学意义（P>0.05）。**结论**　在PD-1抑制剂联合化疗的基础上加用H1RAs，可能为晚期LSCC患者带来更优的生存获益，且不增加总体不良反应。

关键词： H1受体阻滞剂；程序性死亡受体-1抑制剂；肺鳞状细胞癌；免疫治疗；化疗；总生存期
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Abstract: Objective　To investigate the efficacy and safety of H1 receptor antagonists (H1RAs) combined with programmed death protein 1 (PD-1) inhibitor and chemotherapy for advanced lung squamous cell carcinoma (LSCC), so as to provide a reference for the clinical treatment of LSCC. **Methods**　A total of 139 patients with stage Ⅲ-Ⅳ LSCC in the First Affiliated Hospital with Nanjing Medical University from January 2020 to September 2022 were retrospectively enrolled. Sixty-nine patients in the treatment group received H1RAs combined with PD-1 inhibitors and chemotherapy, while 70 patients in the control group were treated with PD-1 inhibitors plus chemotherapy. All patients were followed up until June 30, 2025. The overall survival (OS) of the two groups was analyzed, along with progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR) in the first-line treatment subgroup, and the safety profile of the total population. **Results**　There was no statistically significant difference in baseline data between the two groups (P>0.05). Each group had 60 cases as first-line treatment. The median OS in the treatment group was significantly longer than that in the control group (19.7 months *vs* 16.3 months, P=0.018). The median PFS in the first-line treatment subgroup of the treatment group was also superior to that of the first-line subgroup of the control group (9.4 months *vs* 7.1 months, P<0.01). No statistically significant difference was observed in ORR (63.3% *vs* 55.0%, χ^2=0.862, P=0.353) and DCR (91.7% *vs* 88.3%, χ^2=1.294, P=0.255) between the first-line subgroup of treatment group and the first-line subgroup of control group. The incidence rates of treatment-related adverse

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events (TRAEs) of any grade and grade ≥3 TRAEs showed no statistically significant difference between the two groups (P>0.05). **Conclusion**　The addition of H1RAs to PD-1 inhibitor plus chemotherapy regimen may bring better survival benefits to patients with advanced LSCC without increasing the overall incidence of adverse reactions.

Keywords: H1 receptor antagonists; Programmed cell death protein 1 inhibitor; Lung squamous cell carcinoma; Immunotherapy; Chemotherapy; Overall survival

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肺鳞状细胞癌(lung squamous cell carcinoma, LSCC)是非小细胞肺癌的一个重要亚型。对于不可手术的局部晚期或转移性患者,程序性死亡受体-1(programmed death protein 1, PD-1)抑制剂联合化疗已成为一线治疗的标准方案[1-3],显著改善了患者的总生存期(overall survival, OS)。然而,仍有大量患者发生耐药,因此,探寻能够增强PD-1抑制剂疗效的策略是当前的研究热点。近年来的研究发现,肿瘤微环境中的巨噬细胞、树突状细胞和组胺在免疫调节中扮演着关键角色。组胺通过与免疫细胞上的H1受体结合,促进巨噬细胞极化为M2样免疫抑制表型[4];抑制树突状细胞的成熟和抗原呈递功能,并促进髓源性抑制细胞的聚集,从而建立一个免疫抑制性的微环境[5-7]。临床前研究证实,H1受体阻滞剂(H1 receptor antagonists, H1RAs)能够逆转这种免疫抑制,增强PD-1抑制剂治疗的抗肿瘤效果[8-10]。近期多项在多瘤种实体瘤中的回顾性分析表明,在PD-1抑制剂治疗期间同时使用H1RAs,患者OS和无进展生存期(progression-free survival, PFS)呈现出积极的改善趋势[11-13]。本研究通过一项回顾性队列分析,旨在评估H1RAs联合PD-1抑制剂和化疗治疗晚期LSCC的疗效和安全性。

1　资料与方法

1.1　*临床资料*　本研究为单中心、回顾性队列研究,纳入2020年1月至2022年9月南京医科大学第一附属医院收治的、经病理学确诊为Ⅲ~Ⅳ期不可手术的LSCC患者139例的临床资料。纳入标准:(1) 年龄18~80岁;(2) 美国东部肿瘤协作组(Eastern Cooperative Oncology Group, ECOG)评分为0~2分;(3) 经组织学证实为LSCC;(4) 影像学证实Ⅲ~Ⅳ期,不可手术;(5) 器官功能正常;(6) 接受了至少4个周期的PD-1抑制剂联合化疗;(7) 有完整的临床资料及随访记录。排除标准:(1) 合并其他活动性恶性肿瘤;(2) 合并不稳定的脑或脑膜转移。

根据治疗方案分为治疗组和对照组,治疗组接受H1RAs+PD-1抑制剂+化疗方案,具体为:在PD-1抑制剂联合化疗期间,因任何原因(如过敏、皮疹、瘙痒)规律服用H1RAs(用药时间≥3个月)。对照组仅接受PD-1抑制剂+化疗方案,具体为:在PD-1抑制剂联合化疗期间未使用任何H1RAs的患者。患者及家属均签署治疗方案知情同意书。本研究经南京医科大学第一附属医院伦理委员会审批通过(伦理号:2025-SR-794)。

1.2　*研究方法*　从电子病历系统中收集患者的资料(姓名、性别、年龄、病理诊断、分期、ECOG评分等)、治疗方案、糖皮质激素及抗生素合并用药、疗效评估和不良事件数据。PD-1抑制剂主要为:卡瑞利珠单抗、替雷利珠单抗或信迪利单抗,均为固定剂量200 mg,每3~4周使用(q3~4w)。化疗方案一线用药主要为紫杉醇脂质体(135~175 mg/m^2)、白蛋白型紫杉醇(260 mg/m^2)或紫杉醇聚合物胶束(230~300 mg/m^2)联合卡铂(AUC=5)或奈达铂(80~100 mg/m^2),q3~4w;二线及后线主要为:吉西他滨(1 000 mg/m^2,第1、8天)或多西他赛(60~75 mg/m^2),q3~4w。临床常规止吐预处理方案中单次使用糖皮质激素不纳入统计。

1.3　*随访*　本研究以医院电子病历系统主动监测为主要随访方式,辅以电话随访;随访截止时间:2025年6月30日;对于截止日期前未发生终点事件(疾病进展或死亡)的患者,其生存时间按删失数据处理,以末次联系日期作为随访终点。

1.4　*疗效评估*　肿瘤疗效依据实体瘤疗效评价标准(Response Evaluation Criteria in Solid Tumors, RECIST) v1.1进行评估。所有患者在治疗前(基线)完成影像学(胸、腹、盆腔增强CT)评估,此后每2个治疗周期进行一次疗效评估,直至确认疾病进展、死亡或研究截止。疗效分类如下,完全缓解(complete response, CR):所有靶病灶和非靶病灶消失,且无新发病灶;部分缓解(partial response, PR):靶病灶直径总和较基线减少≥30%;疾病进展(progressive disease, PD):靶病灶直径总和较已记录的最小值增加≥20%,或出现

一个或多个新病灶，或非靶病灶明确进展；疾病稳定（stable disease，SD）：靶病灶缩小未达PR，或增大未达PD。

主要终点为OS，其定义为从患者开始治疗之日起，到因任何原因导致死亡所经历的时间。次要终点涵盖以下几个方面：一线治疗患者的PFS，指从一线治疗开始至疾病发生进展或任何原因导致死亡的时间；一线治疗患者的客观缓解率（objective response rate，ORR），即达到CR和PR的患者在总人群中所占的比例；疾病控制率（disease control rate，DCR），包括达到CR、PR以及SD的患者比例。安全性数据包括治疗相关不良事件（treatment-related adverse events，TRAEs）和免疫相关不良事件（immune-related adverse events，irAEs），根据常见不良反应事件评价标准（Common Terminology Criteria for Adverse Events，CTCAE）v5.0进行分级。

1.5 统计学方法 采用SPSS 22.0软件分析数据，采用Graphpad Prism 10.6软件作图。分类变量以例（%）表示，组间比较采用χ^2检验或Fisher确切概率法检验；连续变量符合正态分布，以$\bar{x}\pm s$表示，采用独立样本t检验比较。生存分析采用Kaplan-Meier法及log-rank检验。采用Cox比例风险回归模型计算风险比（hazard ratio，HR）。P<0.05为差异有统计学意义。

2 结 果

2.1 患者基线特征 共139例患者纳入分析，治疗组69例，H1RAs包括：西替利嗪（9例）、氯雷他定（45例）、地氯雷他定（10例）、枸地氯雷他定（5例）。对照组70例。两组患者在年龄、性别、ECOG评分、治疗线数、肿瘤分期、脑/肝转移比例、PD-L1肿瘤细胞阳性比例分数（Tumor Cell Proportion Score，TPS）、联合放疗比例及合并用药（糖皮质激素或抗生素）方面差异无统计学意义（P>0.05）。见表1。

2.2 疗效结果 中位随访时间为36.5个月。治疗组的中位OS为19.7（95%*CI*：13.7~25.7）个月，显著长于对照组的16.3（95%*CI*：13.7~18.7）个月（*HR*=0.56，95%*CI*：0.38~0.83，P=0.018），见图1A。一线治疗患者共120例，其中治疗组60例，对照组60例，治疗组的中位PFS为9.4（95%*CI*：8.1~10.4）个月，优于对照组的7.1（95%*CI*：6.3~7.6）个月（*HR*=0.53，95%*CI*：0.36~0.76，P<0.01），见图1B。治疗组一线亚组和对照组一线亚组ORR（63.3% *vs* 55.0%，P=0.353）和DCR（91.7% *vs* 88.3%，P=0.255）差异无统计学意义。见表2。

2.3 安全性分析 两组患者的TRAEs见表3。任何级别的TRAEs以及≥3级TRAEs的发生率在两组间差异无统计学意义（P>0.05）。血液学毒性（中性粒细胞减少、血小板减少、贫血）和乏力是两组最常见的不良事件，其发生率组间相似。

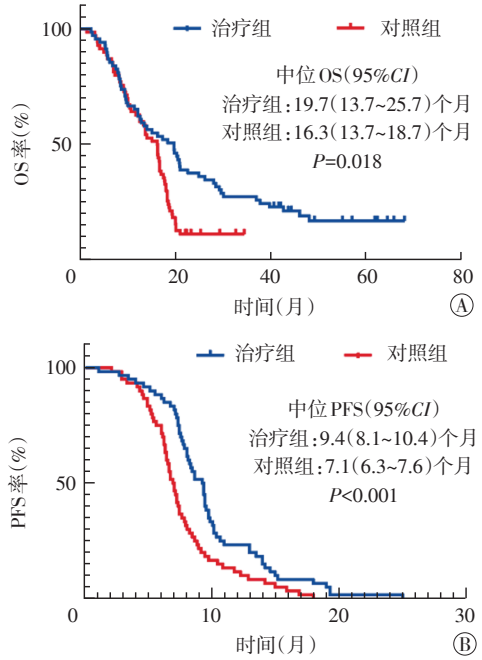
在irAEs方面，两组任何级别irAEs的总发生率相似（60.9% *vs* 65.7%，P=0.553）。任何级别的瘙痒症（26.1% *vs* 1.4%，P<0.01）和皮疹（17.4% *vs* 2.9%，P=0.004）在治疗组中的发生率显著高于对照组。其他常见的irAEs，如天冬氨酸氨基转移酶（aspartate transferase，AST）/丙氨酸氨基转移酶（alanine aminotransferase，ALT）升高、甲状腺功能异常和肺炎发生率两组间差异无统计学意义（P>0.05）。≥3级irAEs及因irAEs导致免疫治疗永久停药的发生的治疗组和对照组差异无统计学意义（11.6% *vs* 21.4%，P=0.119；5.8% *vs* 8.6%，P=0.745）。

表1 两组患者基线特征比较 ［例（%）］

Tab.1 Comparison of baseline characteristics between the two groups ［case（%）］

项目	治疗组（69例）	对照组（70例）	t/χ^2值	P值
年龄（岁，$\bar{x}\pm s$）	66.6±9.4	67.1±7.7	0.338	0.736
性别				
男	61（88.4）	60（85.7）	0.223	0.637
女	8（11.6）	10（14.3）		
ECOG评分				
0~1分	56（81.2）	57（81.4）	0.002	0.968
2分	13（18.8）	13（18.6）		
线数				
1	60（87.0）	60（85.7）		
2	5（7.2）	6（8.6）	0.084	0.959
≥3	4（5.8）	4（5.7）		
分期				
Ⅲ期	32（46.4）	32（45.7）	0.006	0.938
Ⅳ期	37（53.6）	38（54.3）		
脑转移	6（8.7）	7（10.0）	0.700	0.792
肝转移	22（31.9）	25（35.7）	0.228	0.633
PD-L1 TPS水平				
<1%	6（8.7）	5（7.1）		
≥1%	22（31.9）	20（28.6）	0.365	0.833
未知	41（59.4）	45（64.3）		
联合放疗				
是	8（11.6）	10（14.3）	0.223	0.637
否	61（88.4）	60（85.7）		
使用糖皮质激素[a]				
是	8（11.6）	10（14.3）	0.223	0.637
否	61（88.4）	60（85.7）		
使用抗生素				
是	7（10.1）	6（8.6）	0.101	0.750
否	62（89.9）	64（91.4）		

注：[a]表示临床常规止吐预处理方案中单次使用糖皮质激素不纳入统计。



注：A，治疗组和对照组OS曲线；B，两组一线治疗亚组PFS曲线。

图1　两组患者生存曲线

Fig.1　Survival curves of the two groups of patients

表2　一线治疗亚组的肿瘤治疗反应　［*n*=60，例(%)］

Tab.2　Tumor treatment response in first-line therapy subgroups　［*n*=60，case(%)］

组别	CR	PR	SD	PD	ORR(%)	DCR(%)
治疗组一线亚组	0	38(63.3)	17(28.3)	5(8.3)	63.3	91.7
对照组一线亚组	0	33(55.0)	20(33.3)	7(11.7)	55.0	88.3
χ^2值					0.862	1.294
*P*值					0.353	0.255

表3　治疗相关不良事件　［例(%)］

Tab.3　Treatment-related adverse events　［case (%)］

不良事件	治疗组(69例)	对照组(70例)	χ^2值	*P*值
任何级别TRAEs	65(94.2)	68(97.1)		0.441[a]
中性粒细胞减少	25(36.2)	28(40.0)	0.209	0.647
贫血	18(26.1)	20(28.6)	0.108	0.742
血小板减少	12(17.4)	15(21.4)	0.362	0.547
乏力	10(14.5)	13(18.6)	0.419	0.518
≥3级TRAEs	38(55.1)	42(60.0)	0.345	0.557
任何级别irAEs	42(60.9)	46(65.7)	0.351	0.553
瘙痒症	18(26.1)	1(1.4)	17.904	<0.001
皮疹	12(17.4)	2(2.9)	8.104	0.004
ALT升高	8(11.6)	10(14.3)	0.223	0.637
AST升高	7(10.1)	10(14.3)	0.555	0.456
甲状腺功能异常	7(10.1)	9(12.9)	0.251	0.616
肺炎	3(4.3)	6(8.6)		0.493[a]
≥3级irAEs	8(11.6)	15(21.4)	2.434	0.119
因irAE停药	4(5.8)	6(8.6)		0.745[a]

注：[a]采用Fisher确切概率法。

3　讨　论

本研究通过回顾性队列分析，探讨了在接受PD-1抑制剂联合化疗的晚期LSCC患者中，联合使用H1RAs对疗效和安全性的影响。结果显示，与单纯免疫联合化疗相比，加用H1RAs的患者在OS和一线亚组的PFS方面均获得显著改善；两组在ORR和DCR上差异无统计学意义，安全性分析显示加用H1RAs未增加TRAEs的发生风险。

近年来，免疫检查点抑制剂联合化疗已成为晚期LSCC的标准一线治疗方案[1-3]，但仍有相当比例的患者面临原发或继发性耐药。因此，探索能够逆转免疫抑制微环境、增强免疫治疗效果的策略具有重要临床意义。前期基础研究与临床回顾性证据发现H1RAs可能通过拮抗组胺与H1受体结合，改善肿瘤免疫微环境，从而增强PD-1抑制剂的疗效。组胺可通过H1受体抑制巨噬细胞、树突状细胞功能，促进髓源性抑制细胞聚集，形成免疫抑制状态[4-6]。H1RAs则可能逆转这一过程，恢复T细胞介导的抗肿瘤免疫应答。这一机制假设得到了临床观察的支持：近期在多种实体肿瘤中的回顾性分析均发现，在接受PD-1抑制剂治疗时联合使用H1RAs，与患者OS及PFS的改善趋势相关[14-16]。

本研究结果进一步验证了上述观点。在整体人群中，治疗组的中位OS较对照组延长3.4个月(19.7个月 *vs* 16.3个月)，*HR*为0.56，具有统计学意义。在一线治疗亚组中，治疗组的中位PFS亦显著优于对照组(9.4个月 *vs* 7.1个月)。这些临床结果与前期基础及回顾性研究证据一致，共同支持H1RAs可通过拮抗H1受体改善肿瘤免疫微环境，从而增强免疫治疗疗效的观点[17-19]。

在安全性方面，两组间任何级别及≥3级的TRAEs的发生率差异均无统计学意义，提示联合H1RAs并未增加化疗或PD-1抑制剂治疗的整体毒性负担。值得注意的是，尽管治疗组中任何级别瘙痒症和皮疹的发生率显著高于对照组，这可能与其用于处理过敏症状的用药指征有关。≥3级irAEs的发生率在治疗组中数值上低于对照组(11.6% *vs* 21.4%，*P*=0.119)，这一观察值得进一步关注，但其临床意义及与H1RAs的相关性尚需未来研究明确。

本研究的局限性包括其回顾性设计、样本量有限以及潜在的混杂因素，可能影响疗效评估。需要指出的是，本研究治疗组使用了西替利嗪、氯雷他定、地氯雷他定等多种H1RAs，用药指征包括过敏、皮疹等多种原因。不同药物的亲脂性、受体选择性及免疫调节活性可能存在差异，这种异质性可能对疗效的一致性产生影响，由于各亚组病例数有限，本研究未按具体药物进行亚组分析，未来研究应尽可

能统一药物种类以增强结论的可靠性。尽管如此，本研究为“老药新用”提供了初步临床证据，支持H1RAs作为PD-1抑制剂治疗增敏剂的潜在价值。未来有必要开展前瞻性随机对照研究，进一步验证H1RAs在晚期LSCC PD-1抑制剂联合化疗中的增敏作用。

利益冲突　无

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