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# Effect of AGEs-RAGE system on the efficacy of PD-1 inhibitors in the treatment of driver-gene mutation negative advanced non-squamous non-small cell lung cancer

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**ABSTRACT**

To observe the therapeutic effect of PD-1 inhibitors on driver-gene mutation negative advanced non-squamous non-small cell lung cancer (nsNSCLC) and the role of the AGEs-RAGE system in the disease, provide more reliable treatment for future nsNSCLC patients. In this study, we selected 130 nsNSCLC patients admitted between January 2021 and April 2022 were selected as the study subjects, 61 of whom received pemetrexed plus carboplatin (control group) and 69 received PD-1 inhibitors, pemetrexed and carboplatin (research group). The clinical efficacy and adverse reactions of the two groups were compared, and the prognostic survival time was calculated. The results show that two groups were not statistically different in objective response rate (ORR) and incidence of adverse reactions, but the disease control rate (DCR) was higher in the research group ($P$<0.05). Besides, the median progression-free survival (PFS) was prolonged in the research group compared with the control group ($P$<0.05). In addition, changes in the levels of T lymphocyte subsets, AGEs and RAGE before and after treatment were detected, and the relationship between AGEs-RAGE and the therapeutic effect of PD-1 inhibitors was analyzed. The research group also showed higher $CD3^+$, $CD4^+$ and lower $CD8^+$, AGEs and RAGE levels than the control group after treatment ($P$<0.05). Finally, we found that in addition, the efficacy of the study group was inversely related to AGEs and RAGE levels ($P$<0.05). With these results, we concluded that PD-1 inhibitors are effective in the treatment of driver-gene mutation negative advanced nsNSCLC, and the AGEs-RAGE system may provide a more reliable guarantee for the treatment outcomes of patients in the future.

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## Introduction

Lung cancer (LC) is one of the most prevalent malignant neoplastic diseases clinically, with extremely high morbidity and mortality, which adversely influences the life, health and even life safety of patients (1). According to the survey report in 2016, the global average new LC cases exceeded 800, 000 annually, of which 300, 000 died (2, 3). As indicated by clinical statistics, over 80% of LC patients are classified as non-small cell LC (NSCLC), of which 41% are non-squamous NSCLC (nsNSCLC) (4). The clinical feature of LC lies in the concealment of early symptoms, so much so that most patients have progressed to the advanced stage of the disease once diagnosed, missing the best opportunity for treatment (5). In recent years, immunotherapy, which can shift the main target of tumor therapy from tumor cells to the host itself, has attracted wide attention in tumor treatment, with programmed cell death-1 (PD-1) inhibitors being representative drugs (6). As a kind of immune sentinel monoclonal antibody, PD-1 inhibitors have been shown to significantly improve patients' immune function and reduce chemotherapy-induced adverse reactions (7). At present, PD-1 inhibitors have shown strong anti-tumor activity in the treatment of LC, thyroid carcinoma and renal cell carcinoma (8-10), but their application in the treatment of driver-gene mutation negative nsNSCLC has been rarely reported.

On the other hand, the AGEs-RAGE system is a novel tumor immunotherapy pathway proposed by researchers in recent years, in which the key molecules AGEs and RAGE have been well documented to be closely associated with multiple malignant tumor diseases, and their activation can intensify the inflammatory response of tumor cells and immune blockade (11, 12). Therefore, it is clinically considered that blocking AGEs-RAGE expression can not only effectively curb the malignant progression of tumors, but also enhance the killing effect of chemotherapy drugs on tumor cells in the future (13). However, the scheme is still in the theoretical stage, lacking the evidence of clinical research, and the basis of realizing its clinical application is to thoroughly understand the relationship between the AGEs-RAGE system and malignant tumors.

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Accordingly, this study analyzes the therapeutic effect of PD-1 inhibitors on driver-gene mutation negative advanced nsNSCLC while preliminarily exploring the role played by AGEs-RAGE in the disease, aiming at providing more reliable treatment guidance for nsNSCLC with an increasing incidence at present.

## Materials and Methods

### Participants and general data

One hundred and thirty nsNSCLC patients admitted between January 2021 and April 2022 were selected as the study subjects, 61 of whom received pemetrexed plus carboplatin (control group, CG) and 69 received PD-1 inhibitors, pemetrexed and carboplatin (research group, RG). Patient clinical data, shown in Table 1, were not statistically different between groups (P>0.05). The guidelines laid down in the Declaration of Helsinki were strictly followed, and all participants signed the informed consent form.

### Eligibility and exclusion criteria

Eligibility criteria: (1) Meeting the diagnostic criteria for NSCLC according to the TNM Staging and Grading Criteria for Lung Cancer (14), and confirmed diagnosis of metastatic or recurrent (stage IV) nsNSCLC by histology or cytology. (2) Tested positive for driver gene mutations such as ROS1, ALK, and EGFR. (3) Presence of at least one measurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST). (4) Age: 18 ≤ age ≤ 80. (5) No history of systemic anti-tumor therapy. (6) Normal function of major organs. (7) Complete clinical data. Exclusion criteria: (1) Other malignancies (excluding malignant tumors that have been cured, such as non-melanoma skin cancer and cervical carcinoma in situ). (2) Patients with interstitial lung disease or a history of non-infectious pneumonia in recent one year, requiring glucocorticoid therapy. (3) Uncontrolled or severe diseases. (4) Carcinomatous meningitis, spinal cord compression, or brain or pia mater lesions diagnosed by MRI, CT and other imaging examinations. (5) Factors that affect oral administration such as intestinal obstruction, chronic diarrhea, inability to swallow, etc. (6) History of systematic anti-tumor therapy, including traditional Chinese medicine therapy, chemotherapy and radiotherapy.

### Methods

CG: Pemetrexed (H20103287) and carboplatin (H20020180) were used for treatment. Pemetrexed was given depending on the surface area of the lesion, with a standard of 500 mg/m$^2$. After dilution with appropriate glucose solution, pemetrexed was administered intravenously for more than 10 min at a time. Carboplatin therapy was given 30 min after pemetrexed intravenous infusion, with the standard dosage of 300 mg/m$^2$ (diluted with glucose solution) and the infusion time of > 120 min. After the completion of each combination chemotherapy, patients were given an appropriate amount of saline drip and oral folic acid/multivitamin supplements (H10970079) as prescribed. RG: On the basis of CG, Camrelizumab for Injection (S20190027) was added, which was administered 30 min after carboplatin intravenous infusion. Specifically, 200 mg/time of Camrelizumab was redissolved with 5 mL of sterile water for injection and then mixed with 100 mL of glucose solution for intravenous infusion, with the drip time controlled within 30-60 min. Both groups received two three-week courses of treatment.

### Response evaluation

Referring to the RECIST (15), the curative effect was classified as progressive disease (PD), stable disease (SD), partial remission (PR), and complete remission (CR). Objective response rate (ORR) = (PR+CR) cases/total cases × 100%; disease control rate (DCR) = (SD+PR+CR) cases/total cases × 100%. Toxicity was evaluated by referring to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 developed by the National Cancer Institute (NCI). The adverse events mainly included nausea and vomiting, hemoptysis, hypertension, fatigue, loss of appetite, anemia, and thrombocytopenia.

### Sample collection and testing

Fasting venous blood was collected from patients before and after treatment to determine the levels of T lymphocytes CD3$^+$, CD4$^+$ and CD8$^+$ using a Flow cytometer, and the CD4$^+$/CD8$^+$ ratio was calculated. In addition, AGEs and RAGE levels were quantified by PCR. Methods: Total RNA was extracted by Trizol, and cDNA was obtained by reverse transcription. Reaction parameters: 94℃ for 4min, 94℃ for 30s, 56℃ for 30s, and 72℃ for 30s, for 40 cycles. AGEs and RAGE mRNA levels relative to β-actin were calculated by $2^{-\triangle\triangle CT}$. See Table 2 for the primer sequences of this study.

### Outcome measures

The clinical efficacy and the incidence of adverse reac-

**Table 1.** Basic information of patients.

| Group | Male | Female | Age | Phase III | Phase IV | Smoking | No smoking |
|---|---|---|---|---|---|---|---|
| Control group (n=61) | 46 (75.41) | 15 (24.59) | 64.79±4.73 | 30 (49.18) | 31 (50.82) | 38 (62.30) | 23 (37.70) |
| Research group (n=69) | 50 (72.46) | 19 (27.54) | 65.61±5.32 | 31 (44.93) | 38 (55.07) | 46 (66.67) | 23 (33.33) |
| $\chi^2$ (t) | 0.146 | | 0.357 | 0.235 | | 0.271 | |
| P | 0.703 | | 0.925 | 0.628 | | 0.603 | |

**Table 2.**Primer sequences.

| | F (5'-3') | R (5'-3') |
|---|---|---|
| AGEs | GAACCTCCATAATGTCACCAAGC | GTCTGCTCATCCACCATCTTCAG |
| RAGE | GAACCGTAACCCTGACCTG | GCCTTTGCCACAAGATGAC |
| β-actin | CGTGACATTAAGGAGAAGCTG | CTAGAAGCATTTGCGGTGGAC |

tions during treatment were analyzed, and the prognostic survival was counted. In addition, changes in T lymphocyte subsets and AGEs and RAGE before and after treatment were compared between groups, and the relationship between AGEs and RAGE levels and therapeutic effects in RG was analyzed.

### Statistical analysis

Data analyses were made by the SPSS24.0 software. Chi-square tests were performed to compare counting data [n(%)]. For measurement data ($\bar{x}\pm s$), the independent samples t-test was employed for between-group comparisons, and the paired t-test was adopted for the comparison before and after treatment within the group. A minimum significance threshold of $P<0.05$ was used.

## Results

### Comparison of clinical efficacy

As shown in Table 3, the ORR after treatment was 42.03% in RG and 36.07% in CG, with no significant difference ($P>0.05$). While the DCR was higher in RG versus CG (84.06% vs. 68.85%), and the difference was statistically significant ($P<0.05$).

### Comparison of treatment safety

As shown in Table 4, nausea, vomiting, thrombocytopenia and myelosuppression were common adverse reactions in both groups during treatment. The overall incidence of adverse reactions in RG and CG was 34.78% and 29.51%, respectively, showing no significant difference ($P>0.05$).

### Comparison of immune function

As shown in Figure 1, the two groups had no marked differences in pre-treatment levels of T lymphocyte subsets ($P>0.05$). After treatment, $CD3^+$ and $CD4^+$ in both groups decreased, with more marked decreases in RG; while $CD8^+$ increased and was higher in RG compared with CG ($P<0.05$). In contrast, there was no difference in $CD4^+/CD8^+$ between the two groups after treatment ($P>0.05$).

### Comparison of prognostic survival

As shown in Figure 2, as of May 1, 2023, 17 patients in RG and 22 patients in CG died, with no statistical intergroup difference in overall mortality ($P>0.05$). The median PFS of RG was 10.88 months, higher than that of 9.87 months in CG ($P<0.05$).

### Comparison of AGEs and RAGE

As shown in Figure 3, no notable differences were observed in pre-treatment AGEs and RAGE between RG and CG ($P>0.05$). Both groups showed decreased AGEs and RAGE after treatment, with even lower levels in RG ($P<0.05$).

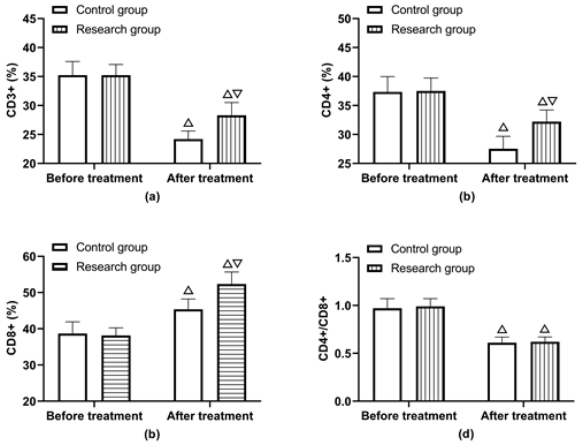


**Figure 1.** Results of the T-lymphocyte subpopulation assay. (a) $CD3^+$, (b) $CD4^+$, (c) $CD8^+$, (d) $CD4^+/CD8^+$. compared with before treatment $^{\triangle}P<0.05$, compared with control group $^{\triangledown}P<0.05$.

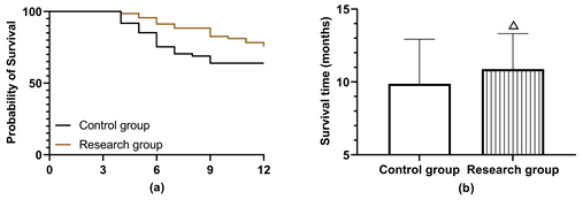


**Figure 2.** Prognostic survival. (a) Prognostic survival curves, (b) Survival cycle comparison. compared with the control group $^{\triangle}P<0.05$.

**Table 3.** Table of clinical outcomes of the two groups of patients.

| Group | CR | PR | SD | PD | ORR | DCR |
|---|---|---|---|---|---|---|
| **Control group (n=61)** | 0 (0.0) | 22 (36.07) | 20 (32.79) | 19 (31.15) | 36.07 | 68.85 |
| **Research group (n=69)** | 2 (42.03) | 27 (39.13) | 29 (42.03) | 11 (15.94) | 42.03 | 84.06 |
| **$\chi^2$ (t)** | | | | | 0.483 | 4.217 |
| **P** | | | | | 0.687 | 0.040 |

**Table 4.** Comparison of the incidence of adverse reactions between the two groups.

| Group | Nausea and vomiting | Thrombocytopenia | Bone marrow suppression | Anemia | Weakness | Hemoptysis | Total incidence |
|---|---|---|---|---|---|---|---|
| **Control group (n=61)** | 4 (6.56) | 3 (4.92) | 2 (3.28) | 4 (6.56) | 4 (6.56) | 1 (1.64) | 29.51 |
| **Research group (n=69)** | 5 (7.25) | 4 (5.80) | 4 (5.80) | 3 (4.35) | 5 (7.25) | 3 (4.35) | 34.78 |
| **$\chi^2$ (t)** | | | | | | | 0.412 |
| **P** | | | | | | | 0.521 |

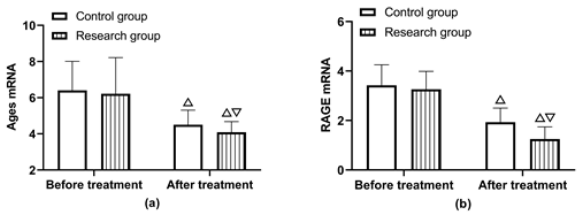


**Figure 3.** Comparison of AGEs and RAGE mRNA. (a) AGEs mRNA, (b) RAGE mRNA. compared with before treatment $^{\triangle}P<0.05$, compared with control group $^{\triangledown}P<0.05$.

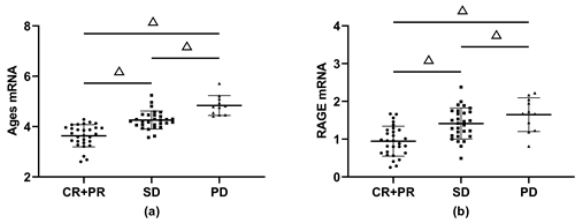


**Figure 4.** AGEs and RAGE with therapeutic effects of PD-1 inhibitors. (a) The relationship between AGEs and the efficacy of PD-1 inhibitor therapy, (b) The relationship between RAGE and the efficacy of PD-1 inhibitor therapy. $^{\triangle}P<0.05$.

### Correlation of AGEs and RAGE with therapeutic effects of PD-1 inhibitors

The patients in RG were grouped according to their clinical efficacy, and the differences in post-treatment AGEs and RAGE expression levels between groups were identified. As shown in Figure 4, AGEs and RAGE were the lowest in CR+PR patients and the highest in PD patients, with those of SD patients in between ($P<0.05$).

## Discussion

At present, immunotherapy, anti-angiogenesis, gene targeted therapy, radiotherapy and chemotherapy are the most commonly used treatments for nsNSCLC, and with the continuous development of precision medicine, the treatment of NSCLC has become more detailed and refined (16). For patients with driver gene mutation negative advanced nsNSCLC, the treatment is mostly based on chemotherapy drugs, combined with immunotherapy and anti-angiogenesis targeted drugs; however, long-term chemotherapy will seriously damage the immune function of patients and lead to a poor prognosis, so how to improve the curative effect and prolong patient survival has become one of the research hotspots (17, 18).

Compared with chemotherapy, PD-1 inhibitors can further improve the anti-tumor immune response ability of patients while playing an indirect killing effect on tumor cells, with potent and sustained clinical response (19). Related studies have shown that PD-1 inhibitors validly increase the survival rate and prolong the survival of patients with advanced NSCLC, making them an important drug for the first-line treatment of advanced NSCLC (20). In recent years, anti-angiogenic drugs have attracted growing attention in the treatment of tumor diseases, as they can not only effectively improve the tumor microenvironment, but also further enhance the tumor immune response to increase the efficacy of tumor immunotherapy (21). Camrelizumab, a PD-1 monoclonal antibody with the characteristics of selectivity and high affinity, is also an endogenous drug as it is synthesized from free substances in the human body, which can effectively bind with $CD4^+$, $CD8^+$ and PD-1 on the surface of some B lymphocytes, thus inhibiting the further transformation and generation of tumor cells (22). Moreover, the drug can further activate the function of macrophages, increase the phagocytosis of tumor cells by the immune system, and help the body rebuild the immune function, playing an anti-cancer and cancer suppressor role (23). In this study, $CD3^+$ and $CD4^+$ of both groups were found to be decreased after treatment, with even lower levels in RG; while $CD8^+$ increased and was higher in RG than in CG. It suggests that PD-1 inhibitors have a certain protective effect on immune function, which is also consistent with previous studies (24) and can support our view. In terms of clinical efficacy, although no significant marked difference was identified in ORR between the two groups, RG had a higher DCR and a longer median PFS than CG, indicating that PD-1 inhibitors can improve the chemotherapy effect of nsNSCLC. We believe that the key is that the use of Camrelizumab can organically bind to PD-1 receptors to block the interaction between PD-1 and its ligands, PD-L1 and PD-L2, and promote the rapid release of immune response inhibition mediated by the PD-1 pathway, thus inhibiting tumor growth (25). Therefore, the malignant growth of tumors can be inhibited and the chemotherapy effect of pemetrexed and carboplatin can be enhanced, resulting in obviously improved clinical efficacy (26). However, CR is still difficult to achieve in patients because the subjects included in this study were all in the advanced stage, with serious and malignant infiltration found in most of the tumors. It also suggests that the treatment of advanced malignant tumors is also a research focus worthy of further exploration. Finally, there is no difference in the incidence of adverse reactions between RG and CG, demonstrating that PD-1 inhibitors have stable safety in the treatment of nsNSCLC and are recommended for clinical use.

On the other hand, the AGEs-RAGE system has been hailed as a breakthrough in the future treatment of malignancies (27), and understanding its role in nsNSCLC as soon as possible will provide a more reliable guarantee for the life safety of patients. In this study, AGEs and RAGE decreased in both groups after treatment, which initially supports the relationship between AGEs-RAGE and nsNSCLC. In RG, we observed more significant decreases in AGEs and RAGE and identified a close relationship between their levels and clinical efficacy (the better the curative effect, the lower the AGEs and RAGE), indicating that the AGEs-RAGE system also has important potential significance in PD-1 inhibitor-based treatment in the future. Previous studies have shown that AGEs can activate a variety of signal transduction pathways related to cell proliferation and apoptosis through interaction with RAGE, including P2l ras, ERK1/2, P38 MAPK, SAPK/JNK, and NF-κB. AGEs interact with RAGE to promote the production of oxidative stress that induces DNA damage, which in turn further promotes the formation of AGEs and up-regulates the expression of RAGE, forming a vicious circle (28, 29). In addition, the increased AGEs-RAGE-mediated reactive oxygen species can activate multiple signal pathways related to cell proliferation and apoptosis, ultimately promoting the occurrence and deve-

lopment of tumors (30). After inhibiting AGEs-RAGE, these malignant growth behaviors of tumor cells can be effectively blocked, thus delaying or even reversing their pathological development. We believe that this is also the main reason for the decreased levels of AGEs and RAGE in patients with better curative effects in this study. But the relevant results will be validated after increasing the sample size, as we counted CR and PR patients together due to the small number of CR patients.

However, this study only analyzed the use of Camrelizumab, and the effects of other PD-1 inhibitors on nsNSCLC need further research. Besides, there is still a lack of available clinical guidelines for the use of the AGEs-RAGE system, and more basic experiments need to be carried out as soon as possible to confirm the mechanism of AGEs-RAGE in nsNSCLC. Moreover, we need to follow up on the subjects of this study for a longer period to evaluate the patient long-term prognosis.

## Conclusion

PD-1 inhibitors are effective and safe in the treatment of driver-gene mutation-negative advanced nsNSCLC and can effectively prolong the life cycle of patients, which is recommended for clinical use. In addition, AGEs and RAGE are closely related to the clinical efficacy of patients, and the use of the AGEs-RAGE system in the future may provide a more reliable guarantee for the improvement of treatment effects and prognostic safety in patients with nsNSCLC.

## Author Contributions

The authors confirm their contribution to the paper as follows: study conception and design: H.Q; data collection: G.W, X.S, G.S; analysis and interpretation of results: Y.F, L.W; draft manuscript preparation: X.L. All authors reviewed the results and approved the final version of the manuscript.

## Availability of Data and Materials

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

## Ethics Approval

The study was approved by the Ethics Committees of The 2nd Affiliated Hospital of Harbin Medical University(Approval Number:2014-022).

## Conflicts of Interest

The authors report no conflict of interest.

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