An advanced IVB lung adenocarcinoma patient with KRAS mutations, benefited from camrelizumab combined with anti-angiogenic agents for therapy: a case report

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Abstract

Purpose: Although the presence of Kirsten rat sarcoma virus (KRAS) mutations predicts of a lack of benefit from epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) therapy for none small cell cancer (NSCLC), it may be more sensitive to programmed combination therapy with cell death 1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitors + anti-angiogenesis. Recent treatment guidelines and clinical studies related to adenocarcinoma in NSCLC have indicated that in patients with inoperable stage IV lung adenocarcinoma, immune checkpoint inhibitors in combination with anti-angiogenic drugs may exert a synergistic effect and significantly improve the efficacy of near-term treatment, but quantification and long-term follow-up of specific clinical indicators are still lacking. No previous cases of long-term good results with camrelizumab combined with anti-angiogenic agents for KRAS-mutated NSCLC have been described. **Methods:** This manuscript reports a case where patients with advanced NSCLC with pleural effusion and KRAS mutations treated poorly with conventional chemotherapy had long-term (more than 18 months) benefit with immunotherapy combined with an anti-angiogenic inhibitor. In this case, pharmaceutical care of the patient was carried out through therapeutic drug adjustment, compliance, efficacy assessment, and safety evaluation to provide a reference for improving the efficacy and safety of drug therapy in clinical practice. **Results:** As of the last follow-up date (December 2023), overall survival was 27 months and the patient is currently in good general condition with no significant complaints of discomfort. **Conclusion:** ICLs in combination with antiangiogenic therapy may be a therapeutic option for patients with KRAS mutations in advanced non-small cell lung cancer with good persistence.

Introduction

a) Background: Lung cancer is one of the most frequently diagnosed cancers and the leading cause of cancer-related deaths worldwide [1] .Lung cancer, also known as primary bronchial lung cancer, is divided into small cell lung carcinoma (SCLC) and non-small cell lung carcinoma (NSCLC), of which NSCLC accounts for about 85% of all lung cancer types. Adenocarcinoma, a type of NSCLC, is the least associated with smoking and accounts for 40% of primary lung tumors[2]. It is often located in the peripheral part of the lung, which also involves the pleura and forms an associated scarring circle and pleural effusion, and has a poor prognosis. Malignant pleural effusion (MPE) is a common complication of advanced lung adenocarcinoma (LAC) associated with a poor life expectancy[3]. The expression of vascular endothelial growth factor, a factor that has recently been shown to play an important role in the formation of malignant pleural effusions, has increased significantly, leading to the emergence of angiogenesis inhibitors as a key approach to control tumour progression[4].

b) Rationale and knowledge gap: The efficacy of chemotherapy for advanced NSCLC has reached a plateau, and molecular targeted therapy has gradually become a hot topic for scholars. The formation of new blood vessels is one of the main mechanisms of tumor growth and resistance, and it also provides a pathway for tumor cell migration and distant metastasis. The recombinant human vascular endothelial inhibitor, Endostatin, is a novel biologic agent for the treatment of tumors. In addition to regulating VEGF expression, it participates in the regulation of multiple signal transduction pathways, thereby inhibiting tumor angiogenesis[5]. Bevacizumab is a humanized monoclonal antibody that selectively binds to vascular endothelial growth factor (VEGF), inhibiting the formation of tumor neovascularization and playing an anti-tumor role. Unlike conventional cancer treatments, immune checkpoint inhibitors do not attack cancer cells directly, but rather mobilize the immune system to re-identify cancer cells that have escaped surveillance, allowing the immune system to function again. Camrelizumab is a novel human immunoglobulin G4 (IgG4)-based monoclonal antibody (mAb) that blocks pathways associated with PD-1 and PD-L1, deregulates t-cell immunosuppression, and enhances t-cell killing of tumor cells.

Previous studies have confirmed that serum levels of tumor markers such as neuron-specific enolase (NSE), carcinoembryonic antigen (CEA), cytokeratin 19 fragments (CYFRA21-1), carbohydrate antigen 125 (CA125)and carbohydrate antigen 153 (CA153) are significantly higher in lung cancer patients than in patients with benign lung lesions and healthy individuals, and the levels are significantly higher in patients with postoperative recurrence than in patients without recurrence[6, 7]. It indicates that serum tumor markers have an important impact on the prognosis of lung cancer patients, while the treatment effect and 5-year survival rate of lung cancer are related to early diagnosis and early treatment[8]. This is closely related to early diagnosis and early treatment. Imaging examination and histocytological examination are the main means to diagnose lung cancer, but both of them have disadvantages such as low sensitivity and specificity and invasiveness. Tumor markers have a higher sensitivity for tumor diagnosis, in addition, serum specimens are more easily available and less invasive to the body.

c) Objective: Recent treatment guidelines have recommended the combination of immune checkpoint inhibitors and anti-angiogenic drugs for the treatment of stage IV lung adenocarcinoma[9], and clinical trials have evaluated the efficacy of this regimen camrelizumab combined with bevacizumab, but there are no specific clinical indicators. Although current monotherapy with immune checkpoint inhibitors (ICIs) has a manageable safety profile, their efficacy is greatly limited by low response rates. Therefore, scientists have sought various combination therapies in an effort to improve response rates to ICIs. Combination regimens have primarily shown better in vivo clinical activity compared to monotherapy; however, the management of adverse effects is also more problematic. There is still a lack of long-term follow-up evidence to confirm the durable response and survival benefits from combination therapies of ICLs combined with anti-angiogenesis.

Based on this background, this case adjusted camrelizumab in combination with recombinant human vascular endothelial inhibitor to camrelizumab in combination with bevacizumab for stage IV lung adenocarcinoma and continued long term follow up, which is reported in detail below.

Case Presentation

In December 2020, a male patient presented with symptoms of cough, sputum and chest tightness for one month and worsened over one week. Ultrasound showed a large pericardial effusion, hypoechoic nodules measuring approximately 31*40 mm (Figure1) and a small amount of pleural effusion, and a diagnosis of NSCLC (adenocarcinoma of the lung) with tumor stage IVB (T3N3MIC) was considered after puncture biopsy of the corresponding site. Next-generation sequencing-based genomic testing showed the result that a mutation in KRAS Q61H was carried out by the patient (Table 1). Immunohistochemical results: Cytokeratin 7 (CK) 7 (+), Cytokeratin20 (CK20) (-), Carcinoembryonic antigen (CEA) (weak +), Transcription termination factor (TTF-1) (+), Napsin-A (+), P63 (An oncogene) (few +), Ki67 (A protein encoded in humans by the MKI67 gene (an antigen recognized by the monoclonal antibody Ki-67) (about 30% +), P53 (An oncogene) (part +). The patient was in good health, denied any history of chronic medical conditions such as hypertension, diabetes and family history of tumors, and admitted to a history of smoking, 20 cigarettes/day, for over 30 years. In March 2021, when the patient was scheduled for his fifth chemotherapy treatment, a

chest CT revealed an increase in pleural thickening, an increase in peripheral inflammation and a significant increase in pleural effusion after 3 months of using cisplatin (100mg) and pemetrexed (800mg) (AP scheme) in combination with endothelial inhibitors. The diameter of the tumor was 39mm ×36 mm (Figure 1). On 20 April 2021, the patient was admitted to the hospital with dyspnea and was diagnosed with malignant pleural effusion the treatment regimen was adjusted to the combined treatment of Cisplatin (100mg) and Docetaxel (120mg) (TP scheme) in combination with camrelizumab (200mg) and endostatin (210mg) was administered. On 2 September 2021, reconsidering the progression of the disease the combined treatment of camrelizumab (200mg) and endostatin (210mg) was administered, during this period the patient underwent proton heavy ion therapy 6 times at external hospitals (details not available). On 20 March 2022, while continuing treatment with camrelizumab, an ultrasound-guided biopsy of the thyroid gland and lymph nodes was performed and papillary thyroid cancer was identified. The patient's condition was discussed as multiple primary malignancies (MPMN)[10], which refers to the simultaneous or sequential occurrence of 2 or more primary malignancies in the same body organ, the mechanism of which is currently unknown and perhaps related to the patient's reduced ability to monitor immune function to clear the mutated cells. Given the critical nature of the patient's primary disease at this time, neither the patient nor the physician considered temporary management in relation to papillary thyroid cancer. Serum lung tumour markers were further controlled with targeted therapy. Changes in lung tumour serology during respiratory chemotherapy are shown in Table 2 and imaging reports are shown in Figure 1. The patient's liver and kidney function were monitored regularly during the drug administration, and no significant hepatic or renal adverse effects were observed in this patient. Since the patient had a fatty liver, the patient's lipid profile and liver function were monitored, as shown in Table 3. After 12 cycles of immunotherapy, the patient's dosing regimen was adjusted from camrelizumab (200mg) in combination with endonuclease (210mg) to a combination of camrelizumab (200mg) and bevacizumab (900mg) with a higher recommendation grade according to the relevant clinical treatment guidelines[9]. This patient's dosing regimen was all based on a 21-day dosing cycle, with all antineoplastic drugs administered intravenously, except for recombinant human vascular endothelial inhibitors, which were administered intra-pump. Interestingly within 18 months of immunotherapy, we not only found that the patient's pleural effusion disappeared but also that the levels of several tumour markers tested fell from above normal to normal range. In addition, the primary tumor in the lung did not progress. As of the last follow-up date (December 2023), the overall survival was 27 months.

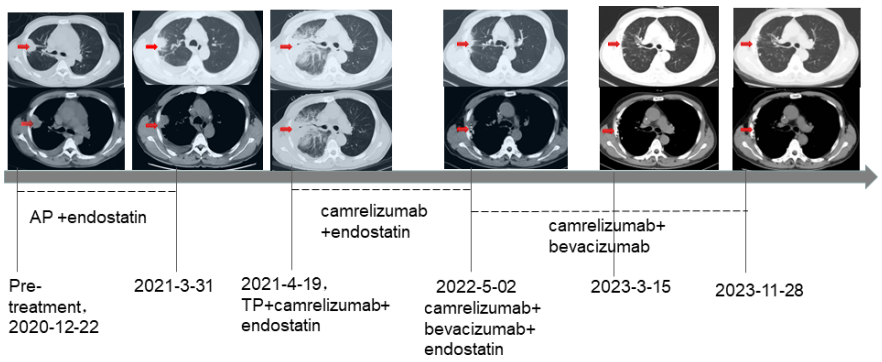

Figure1 . Details of the pathological images and treatments during the course of the disease. Red arrows indicate tumor lesions or nodules.

Table 1. Patient genomic variations information

Gene name	Area covered
EGFR(Epidermal growth factor receptor)	All exon

Gene name	Area covered
ALK(Anaplastic lymphoma kinase)	All exon and intron18-19
ROS1 (ROS proto-oncogene 1, receptor tyrosine kinase)	All exon and intron 31-35
MET (Cellular-mesenchymal to epithelial transition factor)	All exon
KRAS(Kirsten rat sarcoma viral oncogene homolog EGFR: Epidermal growth factor receptor)	All exon

Table 2. Serological indicators of lung tumour during chemotherapy

Serological markers of tumour (normal range)	Pre-treatment	AP (pemetrexed cisplatin) +en
	2020/12/22	2021/3/31
IL-6, pg/ml	157.1	–
SCC (Squamous cell carcinoma-associated antigen), ng/ml (0-1.5 pg/ml)	2.1	0.6
ProGRP (Gastrin-releasing peptide precursor), pg/ml (25.3-77.8 pg/ml)	43.94	26.43
NSE (Neuron-specific enolase), ng/ml (0-16.3 pg/ml)	42.32	15.52
CYFRA211, ng/ml	7.67	3.42
CA199, U/mL (0-25 U/mL)	17.7	20.9
CEA (Carcinoembryonic antigen), ng/ml (0-5 ng/ml)	13.43	43.08
AFP(Alpha-fetoprotein), ng/ml (0-9 ng/ml)	1.96	6.25
CA153, U/mL (0-14 U/mL)	–	34.5
CA125, U/mL (0-35 U/mL)	–	347.3

Table 3 . Monitoring of blood lipids and transaminases during drug administration

Monitoring Indicators (normal range)	camrelizumab+endostatin	camrelizumab+bevaciz
	2021/9/2	2021/12/15
TG(Triglycerides) mmol/L, (0-1.7 mmol/L)	0.95	3.1
TC(Total Cholesterol) mmol/L, (2.85-5.69 mmol/L)	6.15	5.31
AST/ALT (Aspartate Transaminase/Alanine transaminase) (0.8-1.5)	1.8	2.1

The patient went on to pursue a successful career as a staff member in China. After one year of maintenance immunotherapy, he reported no discomfort and this has clearly improved the quality of life. The regimen was maintained as the patient remained symptom-free and the results of the review were satisfactory. According to NSCLC guidelines, bevacizumab in combination with an immune checkpoint inhibitor significantly prolongs progression-free survival and/or overall survival in this disease, and the patient is currently in good

health[9]. As things stand, his risk of lung adenocarcinoma recurrence is low, which is reassuring, especially since his career will require a long-term deployment with limited medical resources. However, if any symptoms of lung adenocarcinoma develop during deployment, then further medical intervention will be necessary.

Discussion

a) Key Findings: In this case, the patient's entire course of treatment covered a comprehensive range of therapeutic measures, with the effects of chemotherapy alone, single PD-1 antibody therapy combined with Endostatin, and dual anti-targeted therapy all being demonstrated. In particular, dual anti-targeted therapy with camrelizumab combined with bevacizumab has already been observed to have better efficacy in 18 months of treatment with no significant adverse effects, providing a new referenceable treatment option for patients with advanced NSCLC with Kras mutation.

b) Strengths and limitations: NSCLC accounts for more than 80 % of lung cancers, the vast majority of which were found to be in advanced inoperable stages. The 2020 guidelines on anti-angiogenesis in advanced NSCLC suggest that platinum-containing chemotherapy combined with anti-angiogenic therapy or immune checkpoint inhibitor immunotherapy is recommended as first-line treatment for patients with advanced non-squamous NSCLC who are negative for driver genes[11]. However, only a small proportion of patients may benefit from treatment with PD-1/PD-L1 antibodies alone, which may be related to the complexity and dynamics of the tumour microenvironment. While previous reports on Endostatin for the treatment of lung adenocarcinoma combined with malignant pleural fluid have mostly been in combination with AP chemotherapy regimens or TKI, this case explored the clinical efficacy of PD-L1 inhibitors in combination with endostatin and dual anti-targeted therapy. In this case, the patient developed more severe malignant pleural fluid after the conventional 5 cycles of AP regimen chemotherapy, so the treatment regimen was adjusted to endostatin and camrelizumab, which was more effective. After more than a year of maintenance treatment with a PD-1 inhibitor in combination with endostatin (during which proton heavy ion therapy was administered to kill solid tumour lesions), the patient's condition stabilized and he was now treated with the newly recommended and clinically proven dual-target therapy regimen for further treatment. After 19 cycles of dual anti-targeted therapy, serum lung tumour markers were further controlled. However, the efficacy of this immunotherapy regimen was not well documented in terms of imaging reports as the patient had undergone concurrent proton-heavy ion therapy to eliminate the tumour lesions.

c) Explanations of findings: The occurrence, development and prognosis of lung cancer are closely related to the immune function status of the body and the tumour immune micro environment[12-14]. Evidence suggests that angiogenesis may be associated with immunosuppression of the tumour microenvironment, thereby enhancing the immune escape of tumour cells. Anti-PD-1 or anti-PD-L1 therapy may improve the sensitivity and prolong the efficacy of anti-angiogenic therapy, and conversely anti-angiogenic therapy may improve anti-PDL1 therapy by supporting vascular changes that contribute to enhanced infiltration and activity of toxic T cells, as well as the destruction of tumour cells so that when high endothelial cell micro vein formation is present in the tumour, the combination of anti-angiogenic inhibitors and checkpoint inhibitors produces a more long-lasting effect when combined with checkpoint inhibitors.

d) Implications and actions needed: Patients were monitored for possible adverse reactions under this treatment regimen by regular routine blood, blood biochemistry, and urinary routine examinations. The patient's renal function was not significantly affected, but the transaminase ratio was high and basically maintained in a stable state. The patient's lipid level was also within the range of concern due to the combination of fatty liver. The patient did not take appropriate lipid-lowering drugs during our treatment, but we cannot exclude the possibility that the patient had related drugs outside the hospital. During the transition treatment (camrelizumab + bevacizumab + endostatin), a significant increase in both triglyceride levels, total cholesterol levels and transaminase ratios were found in this patient, suggesting that the combination of these three drugs may have had some effect on liver function. A combined analysis of efficacy and adverse effect indicators throughout the treatment period revealed that camrelizumab in combination with bevacizumab had significant efficacy and no significant adverse effects. A study of advanced non-small cells

found that the presence of KRAS mutations (G12X, codon 13 and Q61H) was associated with better survival in [?]50% of PD-L1 patients treated with immune checkpoint inhibitor monotherapy, while there was no significant survival difference in patients treated with chemoimmunotherapy[15]. Unfortunately, no data on the classification of KRAS mutation types have been reported. This may be one of the reasons for the better treatment outcome for the patient in this case. Whether all patients with non-small cell lung cancer with KRAS p.Q61H can be treated with this regimen and achieve significant efficacy needs to be further confirmed by more clinical studies.

Conclusions

This case reports a patient with stage IV lung adenocarcinoma treated with a combination of an antiangiogenic inhibitor and an immune checkpoint inhibitor who switched from a combination of camrelizumab and endonuclease to a combination of camrelizumab and bevacizumab with a sustained benefit over 18 months, suggesting that combination immunotherapy may be a treatment option for patients with KRAS mutations in advanced non-small cell lung cancer. Second, the combination of anti-angiogenesis inhibitors and immunotherapy may improve efficacy and with good persistence. Despite encouraging results from studies evaluating the safety and efficacy of this combination therapy, there is currently no head-to-head trial evidence comparing the therapeutic efficacy of ICIs with other therapies such as angiogenesis inhibitors. There is also a need to advance effective immunosurveillance techniques that are closely linked to clinical endpoints. Significant affinities may help to identify favorable immune biomarkers that can then be validated in larger patient cohorts.

Abbreviations

KRAS: Kirsten rat sarcoma viral oncogene homolog

EGFR: Epidermal growth factor receptor

ALK: Anaplastic lymphoma kinase

ROS1: ROS proto-oncogene 1, receptor tyrosine kinase

MET: Cellular-mesenchymal to epithelial transition factor

NSCLC: Non-small-cell-lung-cancer

SCLC: Small-cell-lung-cancer

PD-1/PD-L1: Programmed cell death 1 ligand 1

MPE: Malignant pleural effusion

LAC : lung adenocarcinoma

TKI: Tyrosine kinase inhibitors

VEGF: Vascular endothelial growth factor

MPMN: Multiple Primary Malignant Neoplasm (oncology)

CK7: Cytokeratin 7

CK20: Cytokeratin20

Ki67: A protein encoded in humans by the MKI67 gene (an antigen recognized by the monoclonal antibody Ki-67)

CYFRA21-1: cytokeratin 19 fragments

P53: An oncogene

P63: An oncogene

TTF-1: Transcription termination factor

AP: Chemotherapy regimen of pemetrexed in combination with cisplatin

TP: Combination of paclitaxel-based chemotherapeutic agents with platinum-based agents

IL-6 : Interleukin-6

CA724: Carbohydrate antigen724

SCC: Squamous cell carcinoma-associated antigen

ProGRP: Gastrin-releasing peptide precursor

NSE : Neuron-specific enolase

CA199: Carbohydrate antigen 199

CEA: Carcinoembryonic antigen

AFP : Alpha-fetoprotein

CA153: Carbohydrate antigen 153

CA125: Carbohydrate antigen 125

TG: Triglycerides

TC: Total Cholesterol

AST: Aspartate Transaminase

ALT: Alanine transaminase

Authorship statement

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Patient consent

Written informed consent was obtained from the patient for public cation of this report.

Data availability

The data used to support the findings of this study have been included in this article.

Declaration of competing interest

None.

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