Successful re-challenge of PD-1 inhibitors in combination with bevacizumab and pemetrexed for multiple primary NSCLC progressing on prior PD-1 inhibitor therapy: one case report

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Author contributions
Sheng-Hong Wu and Mei Wang are responsible for the design of the case report, collecting case data and literature for comprehensive analysis, and writing the article. Ying Zhu provided professional opinions on the clinical observation and diagnosis of the case. Zhong-Hui He supervised the entire process of writing the case report, providing professional opinions and guidance to ensure the quality and accuracy of the report.

Competing interests
The authors declare no conflicts of interest.

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Abbreviations
NSCLC, non-small cell lung cancer; PD-1, programmed death factor-1; OS, overall survival; PFS, progression-free survival; ICIs, immune checkpoint inhibitors; ABCP, atezolizumab to bevacizumab, carboplatin, and paclitaxel; CT, computed tomography; MRI, magnetic resonance imaging; IHC, immunohistochemistry; CR, complete remission; PD-L1, programmed cell death-ligand 1; TPS, tissue polypeptide-specific antigen; EGFR, epidermal growth factor receptor; ROS-1, ros proto-oncogene 1; ALK, anaplastic lymphoma kinase; SD, stable disease; PR, partial response.

Citation

Abstract
Lung cancer is a malignant tumor with high incidence and mortality rates in China and worldwide. Approximately 10% of these diseases are caused by multiple primary non-small cell lung cancers (NSCLC). Traditional antitumor therapies, such as chemotherapy, radiotherapy, and targeted therapy, have limited efficacy in the treatment of advanced synchronous multiple primary NSCLC. Immunotherapy is considered the standard of care for advanced or recurrent NSCLC, however, approximately 60% of patients develop primary or secondary resistance to treatment. There are no standard recommendations for overcoming immune resistance. We describe a case of simultaneous multiple primary NSCLC in a patient who received programmed death factor-1 (PD-1) inhibitor monotherapy and developed brain metastases. After receiving second-line treatment with a combination of another PD-1 inhibitor, pemetrexed, and bevacizumab, the patient achieved complete remission, although they experienced grade 3 immune-related adverse reactions. Immune re-challenge is safe and feasible, and choosing a synergistic combination regimen is one of the options to overcome immune resistance. A larger sample size is needed to confirm the effectiveness and safety of this strategy in patients with NSCLC resistant to prior PD-1 inhibitors.

Keywords: NSCLC; brain metastases; PD-1 inhibitor; bevacizumab; pemetrexed; side effect
**Introduction**

Lung cancer is one of the most common cancers and the leading cause of cancer-related deaths in China [1]. Multiple primary non-small cell lung cancer (NSCLC) account for approximately 10% of cases and have a poor prognosis [2]. Platinum-based doublet chemotherapy concurrently with radiotherapy is the standard treatment for advanced NSCLC [3]. Compared with the standard treatment of chemotherapy alone, the addition of bevacizumab to the treatment regimen significantly improved the overall survival (OS), median progression-free survival (PFS), and objective response rate in patients with non-squamous NSCLC [4]. The survival rate of patients with advanced NSCLC has improved significantly with the availability of immune checkpoint inhibitors (ICIs), and treatment strategies have changed [5, 6]. However, drug resistance events inevitably occur. Recent follow-up phase III studies showed that ~60% of patients who initially responded to either ICI alone or in combination with chemotherapy eventually acquired resistance and progressed [7]. There is no clinical consensus regarding the choice of subsequent treatment for this group of patients.

This study reports a successful re-challenge with a programmed death factor-1 (PD-1) inhibitor in combination with bevacizumab and pemetrexed for a case of synchronous dual primary NSCLC that was resistant to prior PD-1 inhibitors alone. This suggests that for specific patients, this regimen could be one of the ways to re-challenge NSCLC after PD-1 inhibitor resistance, and that it may be independent of the pathological type of the tumor and whether it is combined with brain metastases. With the widespread use of ICIs, an increasing number of immune-resistant patients may be considered for this regimen, with further confirms the reliability of this finding. We present the following case in accordance with the CARE reporting checklist.

**Case Report**

A 69-year-old man with a body surface area of 1.8 m² presented with cough for approximately a week and shortness of breath. He had a long history of chronic kidney failure and had been smoked for over 40 years. The patient was not suspected of having cancer and was otherwise healthy. On February 5, 2021, he underwent chest computed tomography (CT), which revealed an occupying tumor in the upper lobe of his right lung (Figure 1A). Other tests performed on the patient, including an emission computed tomography scan, cranial magnetic resonance imaging (MRI) enhancement scan, and an abdominal ultrasound examination, did not reveal any extrathoracic metastases. The tumor markers were below the reference values. After the initial tests, the patient underwent an endobronchial ultrasound biopsy, which revealed the presence of some anisocytic cells in the lymph nodes of the mediastinal 10 R group (Figure 2). Immunohistochemical (IHC) analysis revealed that the cancer was a type of metastatic squamous carcinoma with programmed cell death-ligand 1 (PD-L1) tissue polypeptide-specific antigen (TPS) (IHC 22c3 pharmDx) expression of > 50%. In the lymph nodes of the mediastinal 4 R group, the cancer was identified as a type of metastatic adenocarcinoma with a PD-L1 TPS (IHC 22c3 pharmDx) of 16.2% (Figure 2). Genetic testing revealed that the cancers did not have a specific driver gene mutation. On February 28, 2021, CT-guided pleural biopsy and drainage of pleural effusion were performed. The results of this procedure revealed that the cancer cells were derived from an adenocarcinoma cell line.

Based on these findings, the patient then received two cycles of camrelizumab (Jiangsu Hengrui Medicine Co. Ltd, China) (200 mg d1 Q3W) monotherapy immunotherapy on March 4, 2021, and March 30, 2021, respectively. After the first cycle of drug administration, the patient’s cough, breathing, and chest tightness improved. However, he developed drug-related liver impairment (Grade 3). After discontinuation of the drug, the patient received hepatoprotective treatment. However, on May 19, 2021, he experienced severe nausea and vomiting, and his right leg was weak. An MRI scan showed brain metastasis in the left frontoparietal lobe (Figure 3B). On May 25, 2021, a chest CT scan revealed that the tumors in the thoracic cavity had significantly improved (Figure 1B). The patient was then dehydrated for two weeks to lower the intracranial pressure. However, the intracranial hypertension symptoms did not resolve significantly.

From June 9, 2021, to August 12, 2021, the patient received four cycles of toripalimab (Suzhou Zhonghe Biomedical Technology Co. Ltd, China) (240 mg, day 1) in combination with bevacizumab (Roche Pharma Ltd, Switzerland) (1000 mg, day 1, 15 mg/kg) and pemetrexed (Eli Lilly and Company, USA) (900 mg, day 1, 500 mg/m²) every three weeks. On day 4 after the first dosing cycle, dizziness, nausea, and vomiting completely disappeared, and the muscle strength of the right leg returned to normal. The results showed complete remission (CR) of the tumor after two cycles of treatment and no recurrence after four cycles of treatment (Figure 1 and Figure 3C and Figure 3D). No signs of kidney or liver impairment were detected during treatment. The patient developed a mild rash (grade 2) with pruritus (grade 1) and was treated once with the original treatment regimen on September 7, 2021. A grade 3 rash was observed on various parts of the body, including the scrotal skin. His blood-based biochemical analysis revealed that the level of creatinine level was higher than that at baseline (grade 3). Therefore, the patient discontinued of treatment and supportive therapy and was followed up until April 1, 2023, without disease progression.
REPORT

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Figure 2 Microscopic images of the pathological biopsy viewed at 100 ×. (A) Microscopic images of cytological biopsy of mediastinal lymph nodes (10R); (B) Microscopic images of cytological biopsy of mediastinal lymph nodes (4R); (C) Microscopic images of biopsy tissue of pleural nodes; Immunohistochemical (HE) examination shows positive staining for Napsina (B1), TTF1 (opt 24) (B2) in mediastinal lymph node (4R), and positive staining for Napsina (C1), TTF1 (opt 24) (C2) in the pleural nodes.

Figure 3 Assessment of intracranial lesions during treatment. (A) The baseline cranial MRI images did not reveal an intracranial occupying lesion; (B) The MRI scan after 2 cycles of camrelizumab alone showed a left frontoparietal lobe occupancy accompanied by a significant area of edema formation, which was considered to be a brain metastasis; (C) The MRI scan after two cycles of toripalimab in combination with bevacizumab and pemetrexed demonstrated a CR; (D) The MRI scan after four cycles of the treatment still exhibited the desirable CR. MRI, magnetic resonance imaging; CR, complete remission.

Discussion

Multiple primary NSCLC cases are rare and have poor prognosis [8]. It is impractical to perform a single biopsy of every tumor for simultaneous multiple primary lung cancers combined with multiple intrapulmonary metastases. It is difficult to determine the exact location of cancer and its clinical staging. Overall, synchronous multiple primary tumors are still treated surgically in the early stages, whereas systemic therapy is the mainstay in the late stages [9]. In this case, determining the source of multiple intrapulmonary metastases was challenging, but this did not affect the treatment strategy (cT4N2M1a, stage IVa). As the patient had chronic kidney disease, platinum-based chemotherapy drugs such as cisplatin and carboplatin may aggravate the disease, so they were not considered. Based on the results of genetic testing and the safety and effectiveness of immune monotherapy in patients with advanced NSCLC who have no EGFR, ROS-1, or ALK mutations, PD-1 inhibitor monotherapy was ultimately used as the first-line treatment for this patient. Unfortunately, the patient developed primary drug resistance during treatment. The patient was treated with a PD-1 inhibitor, pemetrexed, and bevacizumab as second-line treatment and achieved CR, although he experienced a grade 3 immune-related adverse reaction. This case led to the hypothesis that this regimen may be a salvage treatment option for NSCLC after ICIs resistance. This finding also implies that PD-1 inhibitors have different degrees of side effects. If a patient experiences severe immune-related side effects after taking one drug, switching to another might be feasible.

Immunotherapy has revolutionized the treatment of advanced NSCLC, and it is regarded as the standard of care for this group of patients [10]. However, the effectiveness of ICI monotherapy and combination chemotherapy was 33%–46% and 45%–75%, respectively, with approximately 40%–60% of patients not benefiting from ICI therapy [11, 12]. A significant proportion of patients treated effectively with ICIs still experience disease progression within 5 years [11]. The reasons for ICIs resistance are complex and dynamically changing [13]. Depending on when the resistance occurs, it can be divided into two types: primary and acquired resistance. ICIs re-challenge as an attempt after immune resistance in metastatic NSCLC. This includes switching to another PD-L1 and finding synergistic combination regimens, such as immune checkpoints (CTLA-4 monoclonal antibody, LAG3 monoclonal antibody, and TIGIT inhibitors), chemothera, radiotherapy, tyrosine kinase inhibitors (Anlotinib, Sitravatinib, Cabozantinib), other targets, or new targets. However, immunotherapy re-challenge after ICIs resistance remains controversial. It has been suggested that immunotherapy failure means that the tumor microenvironment is no longer suitable for immunotherapy and that re-challenge with an immune checkpoint inhibitor may hardly bring any benefit [14]. Several studies found a trend toward benefit in the re-challenge group regardless of whether objective remission was achieved before discontinuation, but the efficacy was very limited and did not reach statistical significance, which may be due to the small sample size [15-17]. A meta-analysis of 442 patients in 15 studies showed that the overall efficacy of ICI re-challenge was worse than that of the first ICI, but some patients achieved SD or PR with re-challenge after initial progression or failure to achieve objective remission, suggesting that re-challenge has some clinical value [18]. According to the progression pattern, the options available for ICI re-challenge vary, and the efficacy obtained varies. Patients who progress due to treatment interruptions due to adverse side effects may benefit from immunotherapy re-challenge in terms of

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PFS and OS [19]. In fact, the safety of ICIs re-challenge should be of greater concern for such patients. A retrospective study showed that ICIs re-challenge was generally safe in patients who relapsed after passive discontinuation due to serious adverse events during treatment [20]. This indicates that there is a benefit of re-challenge after discontinuation compared with permanent discontinuation. Patients with disease progression after 2 years of treatment discontinuation and immunotherapy re-challenge still achieved a CR in 10.3% of patients, while patients with disease progression due to immune resistance had very limited efficacy with subsequent re-challenge treatment with ICIs, only as a trial treatment in the absence of standard regimens [21, 22]. However, for patients with slow progression and those with only oligometastases, ICIs re-challenge can be of continued benefit [23, 24]. Overall, the efficacy of re-challenge with ICIs is closely related to the efficacy of prior immunotherapy received by the patient and the reason for discontinuation.

Based on the imaging findings, only a single symptom of brain metastasis occurred in this patient. For patients with oligometastases, previous studies have shown that PD-1 inhibitors may work better in combination with local therapy [24]. However, there are no clinical studies on whether this protocol is suitable for this case, as patients with symptomatic brain metastases were excluded from the registration trials. Consideration of whole-brain radiotherapy and stereotactic radiosurgery may increase the risk of radionecrosis and radiation-induced white matter leukoencephalopathy [25, 26]. These procedures can worsen the symptoms of cerebral edema, which is not ideal for patients with this condition. A recent study demonstrated that bevacizumab-based therapy is a well-tolerated and effective salvage therapy in these patients [27]. A pooled analysis of the safety and efficacy of the combination of pemetrexed and bevacizumab as second-line treatment in patients with brain metastases revealed that the two agents were well tolerated and showed promising efficacy [28]. The subgroup analysis results of several studies showed that immunotherapy combined with chemotherapy or radiotherapy improved the PFS and OS of patients with stable brain metastases, regardless of the expression levels of PD-L1 [29, 30]. Hence, the addition of bevacizumab to a combination of ICIs and chemotherapeutic agents may be a promising strategy for treating patients with symptomatic brain metastases. In a phase III IMpower150 study, the ABCP (atezolizumab, bevacizumab, carboplatin, and paclitaxel) regimen significantly improved the survival rate of patients with metastatic non-squamous NSCLC in PD-L1 positive subgroups [31]. Based on these findings, immunotherapy combined with chemotherapy and targeted therapy may overcome resistance caused by immune monotherapy.

The success of immunotherapy combined with chemotherapy and targeted therapies in second-line treatment raises another question: which is the best option for patients with PD-L1 expression > 50% PD-1 monotherapy or in combination with chemotherapy? First, the choice of ICIs depends heavily on the level of PD-L1 expression, the tumor mutational burden, the tumor's circulating DNA, and specific genomic alterations. However, reliable predictors of patients who would benefit from chemo-immunotherapy have not been identified [32]. Second, we investigated whether combination regimens can prevent secondary brain metastases in patients with NSCLC. However, the answer to this remains uncertain. The results of the IMpower150 study revealed that approximately 8.3% of patients had new brain metastases [31]. Finally, since no head-to-head studies had compared the effectiveness of different checkpoint inhibitors in combination or alone, it is unclear which approach is better. Although a meta-analysis showed that combination therapy significantly improved PFS and objective efficiency compared with immune monotherapy, there was no significant difference in OS [33]. In addition, the combination regimen is associated with an increased risk of treatment-related adverse effects [34]. These effects were confirmed during treatment in this case. For patients with severe underlying conditions, combination therapy involving immunotherapy and chemotherapy is not considered a suitable treatment. In daily practice, it is important that the decision-making process is personalized according to the patient's condition. This can be achieved by the precise selection of the immune-beneficiary population, dynamic monitoring of ICI therapy, search for synergistic combination regimens, and continuous development of new targets and drugs that could reduce the incidence of drug resistance.

**Conclusion**

Primary or secondary drug resistance may inevitable occur during immunotherapy. This case used a PD-1 inhibitor in combination with bevacizumab and pemetrexed to successfully rescue a case of NSCLC that was resistant to prior treatment with a PD-1 inhibitor. This demonstrates that ICIs re-challenge is safe and feasible, and that choosing a synergistic combination regimen is one of the options to overcome immune resistance. A larger sample size is needed to confirm the effectiveness and safety of this strategy in patients with NSCLC resistant to prior PD-1 inhibitors.

**Ethical Statement**

The authors are accountable for all aspects of this work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Written informed consent was obtained from the patient for the publication of this study and any accompanying images. All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013).

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