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Current Clinical Application of Immune Checkpoint Inhibitors and Anti-Angiogenic Agents in Brain Metastases of Non-Small Cell Lung Cancer

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Abstract: Brain metastasis is a common complication in patients with non-small cell lung cancer (NSCLC). The occurrence of brain metastases has become a challenging issue in the treatment and prognosis of NSCLC. Therefore, identifying the most appropriate therapeutic strategies for patients with brain metastases is essential for prolonging survival. Traditional surgical and radiotherapy approaches have shown limited efficacy, and the blood-brain barrier significantly hinders the penetration of chemotherapeutic agents into the brain. In recent years, immune checkpoint inhibitors (ICIs) have achieved remarkable progress in the treatment of NSCLC. Given that both ICIs and anti-angiogenic agents target the tumor microenvironment, existing evidence supports a synergistic antitumor effect when these agents are used in combination. Furthermore, molecular targeted therapies and ICIs have opened new avenues and treatment options for NSCLC patients with brain metastases. This article discusses the application of immunotherapy and anti-angiogenic agents in NSCLC brain metastases, providing updated therapeutic insights for affected patients.

Keywords: Non-small cell lung cancer; immune checkpoint inhibitors; anti-angiogenic agents; brain metastases

Introduction

Lung cancer (LC) is one of the most common malignant tumors in humans. Based on histopathological classification, it is generally divided into two major categories: non-small cell lung cancer (NSCLC) and small cell lung cancer, with NSCLC being the predominant type, accounting for approximately 85% of cases [1-2]. About 75% of NSCLC patients are diagnosed at an advanced or late stage, and the five-year survival rate remains very low. The high mortality rate is primarily due to local recurrence or distant metastases of the tumor, with the brain, bones, and adrenal glands being the most common sites of distant spread. Patients who develop brain metastases often experience high morbidity

and mortality rates and have an extremely poor prognosis, with a short median overall survival (OS) [3]. At initial diagnosis, 10%–15% of NSCLC patients already have brain metastases, which can lead to various neurological complications [4]. In advanced NSCLC, the incidence of brain metastases ranges from approximately 24% to 44%, with tumors harboring driver gene mutations being more prone to brain metastasis compared to those without such mutations [5]. Clinically, a combination of surgery, whole-brain radiotherapy (WBRT), stereotactic radiotherapy (SRT), and chemotherapy is commonly used to treat NSCLC patients with brain metastases. However, these approaches can often impair neurological function [3]. Targeted therapy has introduced new treatment avenues for NSCLC and has shown potential in prolonging overall survival. According to literature, it has demonstrated certain efficacy in controlling intracranial lesions. Nevertheless, specific targets such as epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) are present in only a small subset of patients. Currently, immunotherapy plays a crucial role in the treatment of NSCLC. Immune checkpoint inhibitors (ICIs), represented by agents targeting cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), programmed death receptor 1 (PD-1), and programmed death-ligand 1 (PD-L1), have emerged as pivotal drugs. ICIs restore the host's antitumor immune response by blocking co-inhibitory signaling pathways [6–7], primarily by relieving immune suppression, reactivating T cells, and inducing tumor cell death. In recent years, ICIs have also shown therapeutic benefits in NSCLC patients with brain metastases, significantly improving prognosis [7]. This paper explores the mechanisms and clinical applications of combining anti-angiogenic agents with immune checkpoint inhibitors in the treatment of brain metastases. The synergistic application of these two therapies has demonstrated strong antitumor effects and the potential to delay resistance development [8].

1. Blood-Brain Barrier Function of the Brain

The blood-brain barrier (BBB) restricts the entry of hydrophilic, systemically administered drugs into the brain. Additionally, the tumor's self-protective mechanisms hinder the achievement of therapeutic drug concentrations in the intracranial space. The BBB's efflux function further impedes drug penetration, resulting in decreased intracranial drug levels. However, brain metastases can disrupt the normal integrity of the BBB [9]. Research indicates that brain metastases larger than 2 mm in diameter can lead to neurological damage, and contrast agent leakage observed during clinical imaging of macroscopic metastases further supports this phenomenon [10]. Radiotherapy has been shown to disrupt the BBB, alter brain cell permeability, and thereby enhance intracranial drug delivery. In the context of NSCLC brain metastases, third-generation cytotoxic agents combined with platinum-based chemotherapy have demonstrated certain therapeutic efficacy [11].

2. Antitumor Mechanism and Clinical Application of Immune Checkpoint Inhibitors

ICIs target molecules such as PD-1, its ligand PD-L1, and CTLA-4. These drugs exert their effects primarily by modulating the tumor microenvironment, suppressing immune checkpoint activity, and reactivating T lymphocytes to restore immune responsiveness against malignant cells [12]. An Italian study investigating the PD-1 inhibitor nivolumab in patients with non-squamous NSCLC reported that, among 409 patients with brain metastases, 4 achieved complete response, 69 achieved partial response, with a median PFS of 3 months and median OS of 8.6 months, suggesting potential benefits of nivolumab in brain metastasis management [13]. A Phase III clinical trial [14] found that advanced NSCLC patients receiving first-line or previously administered monotherapy with the PD-1 inhibitor pembrolizumab demonstrated sustained antitumor activity, significantly improved 5-year survival rates, good tolerability, and acceptable long-term safety with limited evidence of late-onset or new toxicities. A pooled analysis of the KEYNOTE 001/010/024/042 trials [15] revealed that pembrolizumab monotherapy showed efficacy in PD-L1-positive NSCLC patients with brain metastases. However, a retrospective study conducted by Martin et al. [16], which included 480 patients (294 with NSCLC, 145 with melanoma, and 41 with renal cell carcinoma), found that among 115 patients treated with combined therapy, 38 who received SRT experienced adverse reactions, with a high incidence of radiation necrosis. While ICIs have demonstrated the potential to prolong

survival in patients with brain metastases, selecting the appropriate patient population and optimal therapeutic regimen requires further investigation. A more rational treatment approach and the development of precision oncology strategies are necessary to maximize survival outcomes in this patient population.

3. Mechanisms and Clinical Applications of Anti-Angiogenic Agents

Vascular endothelial growth factor (VEGF) is the most critical pro-angiogenic factor in the process of neovascularization. It promotes the formation of new blood vessels and increases vascular permeability, thereby facilitating tumor metastasis. VEGF is expressed in both small cell lung cancer and NSCLC, and its overexpression is associated with poor prognosis in lung cancer. Furthermore, VEGF can inhibit apoptosis of endothelial cells by inducing the expression of Bcl-2.

3.1 Bevacizumab

Bevacizumab, a clinically common anti-VEGF monoclonal antibody, binds with high affinity to all isoforms of VEGF and prevents its interaction with endothelial cell surface receptors. This blocks VEGF signaling pathways, reduces VEGF activity, inhibits angiogenesis, decreases vascular permeability, and suppresses tumor growth. A retrospective study [17] demonstrated that bevacizumab combined with platinum-based chemotherapy significantly improved the prognosis of patients with advanced adenocarcinoma and brain metastases. Jiang et al. [18] reported that in a cohort of 208 NSCLC patients with EGFR mutations, those treated with bevacizumab combined with EGFR-TKIs (experimental group) had significantly prolonged progression-free survival (PFS) and OS compared to those treated with EGFR-TKIs alone (control group).

3.2 Small Molecule Anti-Angiogenic Drug – Anlotinib

Anlotinib is a multi-target tyrosine kinase inhibitor (TKI) that effectively inhibits several receptor tyrosine kinases, including VEGF receptors. It blocks a variety of enzyme pathways in the body, exerting anti-tumor effects. Notably, it is the only domestically developed oral anti-angiogenic targeted drug for lung cancer in China [19]. A post-hoc analysis of a phase III randomized controlled trial [20] showed that among patients with brain metastases, the intracranial objective response rate (ORR) for the anlotinib group was 14.3%, and the disease control rate (DCR) was 85.7%, with a significant association between anlotinib and delayed intracranial progression. Research by Wu et al. [21] also indicated that anlotinib could reduce intracranial metastatic lesions and alleviate brain edema induced by SRT.

3.3 Endostar (Endu)

Endostar is a domestically developed biological agent that inhibits angiogenesis by preventing endothelial cell migration, thereby suppressing tumor proliferation. Animal studies have shown that endostatin can "normalize" tumor vasculature, improve blood supply and oxygenation in tumors, and enhance the contact between circulating drugs and tumor cells, leading to improved therapeutic outcomes. In a study by Jiang et al. [22], 80 NSCLC patients with brain metastases were randomly assigned to a radiotherapy-only group (control) and a radiotherapy combined with Endostar group (experimental). The combination group showed significantly reduced cerebral edema ($P = 0.003$), especially in VEGFR2-positive patients who responded better to treatment. Zhao Yongli et al. [23] found that in NSCLC patients treated with Endostar, when WBRT at 30 Gy was administered within a specific time window one week after Endostar treatment, brain cell permeability increased. The combination of Endostar and WBRT not only enhanced intracranial drug concentrations but also alleviated cerebral edema and reduced adverse effects.

4. Synergistic Anti-Tumor Mechanisms of Immune Checkpoint Inhibitors and Anti-Angiogenic Agents

4.1 ICI Enhances Anti-VEGF Anti-Tumor Effects via IFN-γ

Following ICI treatment, activated tumor immune response cells continuously secrete a variety of immune cytokines. Some of these cytokines possess direct anti-angiogenic mechanisms and may induce normalization of tumor vasculature [24]. Interferon-gamma (IFN-γ) plays a potentially key catalytic role in this process. IFN-γ, secreted by activated T cells, binds to receptors on tumor endothelial cells, promoting rapid vascular normalization and functional improvement, as well

as regression of abnormal vessels [25–26]. IFN−γ also reduces the secretion of VEGF by tumor−associated fibroblasts, downregulates angiogenesis, and inhibits neovascularization pathways in tumor endothelium, collectively suppressing tumor growth. In murine tumor models, selective inhibition of immune checkpoint receptors such as CTLA−4 and PD−1 directly activates helper T cells, which in turn induces tumor vascular normalization [27]. Therefore, the combination of ICIs and anti−VEGF agents has shown considerable efficacy in adjuvant treatment of advanced NSCLC, significantly improving OS [28–29].

4.2 Anti−Angiogenic Agents Enhance the Immune Effects of Immune Checkpoint Inhibitors

Anti−angiogenic agents bind specifically to VEGF receptors on tumor endothelial cells, blocking the interaction between VEGF and its receptors, which inhibits the formation of new tumor vasculature and reduces oxygen and nutrient supply to tumors. Tumor cells not only secrete immunosuppressive factors but also recruit suppressive immune cells to promote tumorigenesis [32–33]. The process of tumor vascular normalization enhances the antigen−presenting function of dendritic cells (DCs), thereby promoting immune response [30–31]. In essence, vascular normalization aims to weaken the immunosuppressive microenvironment [34]. Anti−VEGF agents work by disrupting the immunoprotective functions of tumor endothelial cells, effectively weakening the tumor's immunosuppressive barriers [35]. The combined use of ICIs and anti−VEGF agents enables mutual enhancement—ICI promotes immune recognition and effector responses, while anti−angiogenic agents help restore an immune−permissive microenvironment—thus reversing tumor−induced immune suppression and improving clinical outcomes [36].

4.3 Summary

The synergy between immune checkpoint inhibitors and anti−angiogenic therapy has demonstrated promising preliminary results [37]. However, extensive clinical trials are warranted to further validate and support their combined therapeutic potential.

5. Future Perspectives

The tumor microenvironment is influenced by a variety of cellular components and signaling pathways, whose interactions are intricate and not yet fully understood. Therefore, the underlying mechanisms of tumor progression and resistance in the context of combination therapy still require further investigation and refinement [38]. One of the key challenges is how to minimize the risk of therapeutic resistance that may arise during combined treatment regimens. Targeted therapies for advanced−stage cancer have now entered a new era of multidisciplinary team (MDT)−based collaborative care. Within this framework, the development of personalized and precision treatment plans tailored to individual patients is crucial for improving therapeutic efficacy and patient satisfaction. Rapid scientific advancements in cancer diagnostics and treatment have been made globally. However, more extensive basic research is essential to assess the benefits and drawbacks of combined treatment strategies, in order to enhance quality of life and extend survival or even achieve long−term remission. This remains a significant and ongoing challenge in the field of oncology.

Patients with brain metastases from NSCLC generally have poor prognosis due to the protective effects of the BBB and intrinsic tumor defense mechanisms, which limit the efficacy of conventional treatments. As oncology moves toward a personalized medicine paradigm, the rapid development of gene sequencing technologies has made targeted therapies increasingly important. Although newer generations of targeted agents have improved metrics such as PFS and OS, the overall clinical benefit for patients remains somewhat limited. The combination of immune ICIs with anti−angiogenic agents represents a promising therapeutic strategy for patients with intracranial metastases from advanced NSCLC; however, a series of more complex challenges remain to be solved.

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