Research progress of anti-angiogenic therapy combined with immunotherapy and radiotherapy for the treatment of brain metastases in non-small cell lung cancer (Review)

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Abstract. The treatment of brain metastases (BMs) from non-small cell lung cancer (NSCLC) is primarily systemic and local; however, the therapeutic effects of various treatment methods on BMs are minimal. The occurrence of BMs from NSCLC is a complex process. The penetration of tumour cells into the blood-brain barrier changes the function of cell junctions, leading to changes in the microenvironment of intracranial tumours. Antitumour therapies such as immunotherapy (IT), chemotherapy, targeted therapy and radiotherapy (RT) all affect the tumour immune microenvironment (TIM). Anti-angiogenic drugs (AADs) normalize blood vessels and improve access to the tumours, which is an effective strategy for combination IT. IT combined with RT improves the survival rate in patients with BMs and reduces the risk of brain failure and nervous system mortality. AADs can markedly alleviate radiation-induced brain injury after RT. Furthermore, anti-angiogenic therapy can regulate the immune checkpoint inhibitor-mediated microenvironment of intracranial tumours. Combining these three factors may improve the prognosis of patients with NSCLC and BMs. However, there is no reliable evidence on the safety and efficacy of their combination therapy. Therefore, the present article reviews the effects of AADs combined with IT and RT on the TIM of patients with NSCLC with BMs and the clinical application progress in order to provide ideas for the treatment of NSCLC with BMs.

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Abbreviations: BMs, brain metastases; NSCLC, non-small cell lung cancer; RT, radiotherapy; SRS, stereoscopic radiosurgery; AAD, anti-angiogenic drugs; IT, immunotherapy; TIM, tumour immune microenvironment; AAT, anti-angiogenic therapy; ICI, immune checkpoint inhibitors; ITR, immunotherapy resistance; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1; DNA, deoxyribonucleic acid; WBRT, whole-brain radiotherapy; SBRT, stereoscopic body radiotherapy; PFS, progression-free survival; OS, overall survival; MDSC, marrow-derived suppressor cell; TAM, tumour-associated macrophage; CTL, cytotoxic T lymphocyte

Key words: NSCLC, immune microenvironment, brain metastases, radiotherapy, anti-angiogenesis, immunotherapy

Contents

1. Introduction

Lung cancer is one of the most common cancers, with a 5-year survival rate of only 27%, and non-small cell lung cancer (NSCLC) is the most common subtype (1). Of note, ~57% of patients with NSCLC are initially diagnosed at an advanced stage and 40-50% of patients develop brain metastases (BMs) during the disease progression due to the limited screening methods (2,3). Currently, the primary treatment of patients with NSCLC with BMs is systemic therapy coupled with local therapy, such as surgery and radiotherapy (RT) (4). For instance, the 2022 American Society of Clinical Oncology-Society for Neuro-Oncology-American Society for Radiation Oncology guidelines (5) recommend that patients with asymptomatic BMs from NSCLC receive stereoscopic radiosurgery (SRS) or stereoscopic body RT alone for treating one to four lesions. RT should be provided after surgery in patients with one or two BMs, because it is indispensable in the treatment of brain metastases. Furthermore, targeted therapy is preferred for patients with BMs that are vital for driver genes,

such as Epidermal Growth Factor Receptor gene mutations can be treated with 1-3 generation targeted drugs. But there is insufficient evidence to recommend any systemic therapy, specifically for intracranial tumour control in patients who are negative for driver genes (4-6). In summary, the current treatments for BMs are limited, which markedly affects the overall prognosis of patients with NSCLC with BMs (7).

Angiogenesis and immune escape are key elements in tumour formation and the growth of metastatic brain tumours in NSCLC is critically dependent on angiogenesis (8). Anti-angiogenic drugs (AADs) normalise blood vessels, improving access to the tumours, which is useful when combined with immunotherapy (IT) methods. This combined treatment may have a synergistic effect on the tumour immune microenvironment (TIM) to inhibit the occurrence of tumours (9-11). In addition, anti-angiogenic therapy (AAT) can modulate the tumor immunosuppressive microenvironment and help to reverse IT resistance (ITR) (12). Previous studies have reported that IT combined with AAT has tolerable toxicity and efficient antitumour activity in patients with advanced NSCLC receiving later-line treatment (13). Furthermore, AADs cause dehydration, which creates conditions for RT to further control tumour progression and effectively improve radiation-induced brain injury (14).

The emergence of IT has become a milestone in antitumour therapy. However, the frequency of ITR is also increasing with the use of immunosuppressants (15). Although the TIM is an abundant source of therapeutic targets (16), the understanding of the TIM in the brain lacks comprehensive and integrated analyses. Nevertheless, the importance of the TIM cannot be ignored in the whole treatment process of patients with NSCLC with BMs (17). Research into the mechanisms will provide a more comprehensive understanding of the treatment of diseases. Accordingly, the present article aimed to elaborate on the TIM and clinical application of AAT, IT and RT in patients with NSCLC with BMs, in order to broaden the ideas for subsequent clinical research and treatment strategy design.

2. Intracerebral immune microenvironment of NSCLC

The occurrence of BMs from NSCLC is a complex process and the TIM serves an indispensable role (18). Studies have demonstrated that monocyte-macrophages, neutrophils, $CD4^+$ T cells and $CD8^+$ T cells serve a decisive role in the TIM of BMs from lung cancer (9,19). When disseminated tumour cells meet these immune cells, complex interactions occur, forming tumour-promoting and tumour-suppressing environments (20). Due to differences in the unique composition of the extracellular matrix in terms of collagen, hyaluronic acid and enzymes, the TIM of the brain has unique characteristics, which are radically different from those of the TIM of primary lung cancer (21). In NSCLC BM, tumour cells change the function of cell junctions after penetrating the blood-brain barrier, which leads to an altered intracranial TIM (22). For instance, patients with lung adenocarcinoma show a more distinctive pattern of low infiltration of $CD3^+$ and $CD8^+$ lymphocytes, suggesting that most patients lack a meaningful local immune response associated with BMs (23,24). An analysis of immunohistochemical results by Kim *et al* (25) showed that the number of programmed cell death protein 1 (PD-1) tumour-infiltrating lymphocytes was markedly lower in BMs compared with primary lung cancer. As shown in Fig. 1, another study revealed that PD-1-positive tumour-infiltrating lymphocytes had low intracranial expression and high primary lung sites in patients with NSCLC with BMs due to their lower permeability. Programmed cell death protein ligand 1 (PD-L1) is generally highly expressed in metastatic sites and is highly expressed in the brain, which is one of the reasons for the application of IT (26). These findings reveal that the efficacy of immune checkpoint inhibitor (ICI) agents is different. In other words, tumors with high PD-L1 expression are more likely to respond to ICI. Besides, chemotherapy, targeted therapy, RT and other antitumour therapies also affect the TIM (27-29).

In 2022, Li *et al* (30) performed ribonucleic acid sequencing on 86 samples from 43 patients with primary lung tumours and corresponding BMs to analyse the TIM. The results revealed that BMs were more immunosuppressed compared with primary lung tumours. In addition, the article by Wang *et al* (31) explored the mechanism of BMs in NSCLC, further highlighting the role of the TIM in the treatment of metastatic tumours. A previous study has concluded that combination therapy can increase the expression of PD-L1 in NSCLC BMs, thereby enhancing the treatment efficacy in these patients (32). In conclusion, in the era of IT, numerous treatment methods have different effects on the intracranial immune microenvironment of patients with BMs. The combined treatment has a synergistic effect and the impact on the microenvironment has become more evident (33,34).

3. RT

RT is an effective local treatment for NSCLC and it can affect the intracranial immune microenvironment. It eliminates tumour cells by inducing double-stranded deoxyribonucleic acid (DNA) damage and regulating antitumour immune responses at both irradiated and non-irradiated sites (35). As a commonly used treatment for BMs, RT can promote tumour-associated anti-immunity and enhance reoxygenation in the TIM, thereby promoting the recruitment of several immune effector cells and helping them infiltrate tumours (36,37). In addition, RT can cause immunogenic cell death and promote the release of tumour associated antigens, thus serving a synergistic role with IT (38). RT combined with IT has shown notable efficacy and can control tumour progression and prolong the survival of patients with NSCLC. Notably, studies have demonstrated that PD-L1 expression is mediated by the PI3K/AKT/mTOR pathway, which controls numerous cellular processes, including PD-L1 translation and transcription (39). Stimulation to enhance the AKT/mTOR pathway increases PD-L1 expression and vice versa. Downstream elements of AKT stimulate gene transcription by binding to the PD-L1 promoter. Furthermore, NF-κB, a downstream signal transducer of AKT, also acts on the promoter to induce PD-L1 mRNA expression (40). RT activates PI3K/AKT signalling through various pathways, such as the DNA damage response, reactive oxygen species (ROS) activation, inflammatory factor expression and growth receptor expression, leading to PD-1 expression and radioresistance (41).

Immunosuppressive agents can eliminate radioresistance caused by the upregulation of PD-L1 induced by RT and

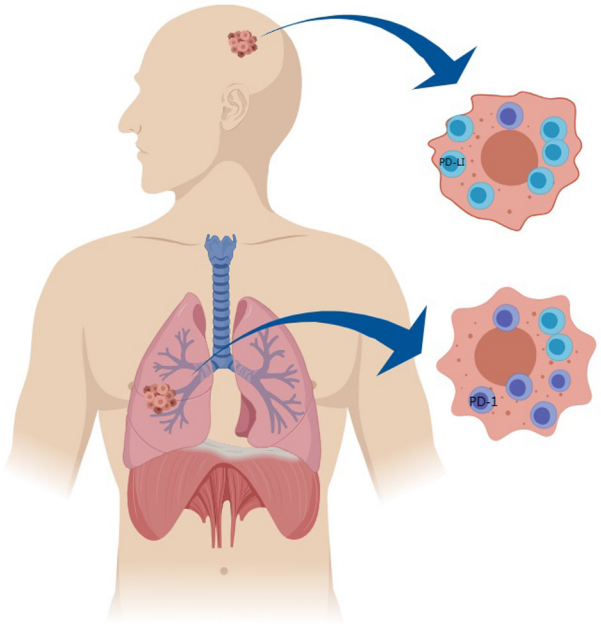

Figure 1. Differences in the immune microenvironment between intracranial and extracranial brain metastases. PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1.

enhance its efficacy (42). Ikarashi *et al* (43) reported that CD4+ T cells, CD8+ T cells and CD4 Foxp3+ T cells were significantly higher in the tumor and stromal regions in primary lung cancer specimens, whereas only CD204+ cells were elevated in the tumor regions of brain metastases. CD4+ and CD4 Foxp3+ T cells were significantly increased in brain metastases with radiation therapy in the cancer and stromal regions compared with patients without radiation therapy. These macrophages may be immunosuppressive and make the immune environment less reactive (44,45).

Combination therapy can increase the local control rate of RT. Whole-brain RT (WBRT) and stereoscopic body RT (SBRT) are effective treatments for NSCLC with BMs, resulting in marked improvements in the local control rate (46). A study suggests RT combined with IT has an improved survival benefit compared with the sequential mode in patients with NSCLC BMs (47). Some data also show that RT combined with IT has a relatively high local intracranial control rate and results in an improved disease prognosis (48). ICIs coupled with RT have a strong intracranial efficacy and show a clinical benefit for patients with EGFR-mutant NSCLC with BMs whose previous EGFR-tyrosine kinase inhibitor (TKI) treatment failed (49,50). A meta-analysis of 32 preclinical and 9 clinical studies revealed that the radiosensitising effect of immunosuppressive agents exhibited a range with sensitizer enhancement ratios from 0.4 to 80, and it was improved when immunosuppressive agents were administered simultaneously (51). In addition, a study reported that RT combined with anti-vascular targeted therapy can also cause immune effects in patients with BMs. For instance, bevacizumab combined with radiotherapy can increase the infiltration of immune cells (52).

Cerebral radiation necrosis is one of the side effects of RT. The primary mechanism is the increased permeability caused by neovascularization, resulting brain edema with symptoms such as dizziness and headache. AAT is one of the most important treatment methods for these patients with cerebral edema (53). Therefore, if radiation-induced brain injury occurs after RT, AAT can be protective (42,54). The mechanism of the synergistic action between AAT and ionising radiation is complex. Drugs that target the tumour vasculature and angiogenesis in new tumours can regulate the TIM and improve blood flow and oxygenation, thereby increasing radiosensitivity (55). Previous studies have demonstrated that bevacizumab is a feasible and favourable supportive treatment for cerebral necrosis after WBRT or SBRT, which can notably relieve patient symptoms and improve RT tolerance (56,57). The results of the meta-analysis by Khan *et al* (58) showed a marked improvement in both radiographic and clinical responses with bevacizumab, without any serious adverse events. In addition, anlotinib can promote vascular normalisation and increase tumour tissue oxygenation, thereby improving the efficacy of radio-surgical treatment (59). Furthermore, it can also increase the infiltration and activation of $CD8^+$ T cells encouraged by RT, promote the cytotoxicity and proliferation of $CD8^+$ T cells, promote the activation of immune memory and enhance radiosensitivity (60). In summary, combination therapy can increase the local control rate of RT.

4. Anti-angiogenesis

AADs influence the TIM of patients with NSCLC with BMs. Animal studies have demonstrated that AAT can reduce the infiltration of intracranial tumour T cells and reduce the number of immunosuppressive tumour-associated macrophages (TAMs) (61). At the same time, it can also decrease the number of blood vessels in tumours, promote the stability of the endothelium, enhance endothelial barrier function, promote the migration of white blood cells and heighten antitumour activity (62). At present, AATs approved for clinical use are mainly classified into three main categories: Small-molecule multitarget angiogenesis inhibitors, large-molecule single-target angiogenesis inhibitors and endogenous pan-target angiogenesis inhibitors (63,64). The role of these drugs has been explored in clinical trials of various diseases, including breast cancer (65), gastric cancer (66) and liver cancer (67). For instance, previous trials have demonstrated that bevacizumab can improve the objective response rate. However, the effects on the progression-free survival (PFS) and the overall survival (OS) were not clinically meaningful in patients with NSCLC with BMs (68,69). A previous study demonstrated that apatinib was effective in patients with advanced NSCLC, but the improvement of PFS was limited (70). However, several larger prospective studies reported that apatinib was effective and well tolerated in patients with advanced NSCLC, and PFS and OS were markedly improved (71,72). Regorafenib can inhibit tumour growth and angiogenesis *in vivo*, enhance the antitumour efficacy of antigen-specific T cells and regulate macrophage polarisation to enhance antitumour immunity (73). In a retrospective study, anti-PD-1 therapy combined with anlotinib had tolerable toxicity and superior antitumour activity in treating patients with advanced NSCLC treated beyond second-line therapy (13). In addition, a number of AADs, such as lenvatinib

and Endostar, have shown beneficial effects on the treatment of lung cancer, but the effects of single drugs on the TIM are relatively unknown (62,74). Therefore, further exploration of the mechanisms of action of different drugs is needed.

AAT enhances the efficacy of combined therapy by affecting the TIM. A preclinical study demonstrated that AAT can induce vascular normalization (75). Therefore, consolidation therapy with AAT after RT is an effective approach (76). AAT restores microvasculature in the tumour, thereby alleviating hypoxia, and its combination with SBRT may synergistically inhibit tumour growth (77). Park *et al* (78) performed further animal experiments and demonstrated that the combination of AAT inhibiting VEGF and placental growth factor and RT could effectively inhibit tumour growth.

Through anti-angiogenesis, tumour vascular normalization and TAM polarisation from the protumour M2 phenotype to the antitumour M1 phenotype occur. Bevacizumab inhibits angiogenesis by increasing perivascular cell coverage and decreasing tumour hyperpermeability, vessel calibre, hypoxia and interstitial fluid stress. This reduces peritumoral oedema and alleviates subsequent radiation necrosis (79). Furthermore, it can inhibit DNA double-strand break repairs, enhance tumour microvasculature recovery and increase NSCLC radiosensitivity (80). For instance, Li *et al* (81) explored the combination of bevacizumab with SRS or WBRT for BMs and found that the combination therapy improved the overall efficacy and reduced peritumoral oedema of BMs caused by NSCLC, without any notable side effects. Chen *et al* (82) also found that the combination of bevacizumab and SRS was effective in the treatment of BMs with improved radiographic response and less treatment-related toxicity. In addition, anlotinib can improve the vascular structure and permeability of tumours and reduce brain oedema, making it a useful alternative to glucocorticoids in treating refractory brain oedema (83). Previous studies on combination therapy have demonstrated that effective low-dose anlotinib combined with PD-1 blockade can induce durable antitumour effects with few side effects (84). Research on the use of anlotinib combined with RT in the treatment of brain malignant tumours has found that RT reduces the effect on the blood-brain barrier, thereby enhancing the antitumour activity of anlotinib (85). Apatinib can improve radiation-induced brain necrosis in patients with head and neck cancer and is well tolerated when combined with RT (86). Sunitinib can inhibit tumour growth and angiogenesis, showing efficient synergistic tumour inhibition ability (87). In conclusion, AAT has clinical importance for treating patients with advanced NSCLC with BMs.

Combination of AADs may contribute to reversing resistance to IT. The tumour vasculature is an essential component of the TIM. Improving access to tumours by vascular normalization with AAT is an effective combination strategy with IT, and this combination therapy may have a synergistic effect on the TIM to inhibit tumour occurrence (9,88,89). As shown in Fig. 2, VEGF can bind to VEGFR on the surface of bone marrow-derived suppressor cells (MDSCs) and promote their continuous proliferation as a chemoattractant. MDSCs are immunosuppressive cells, and anti-VEGF therapy can inhibit their proliferation, enhance the immune response and

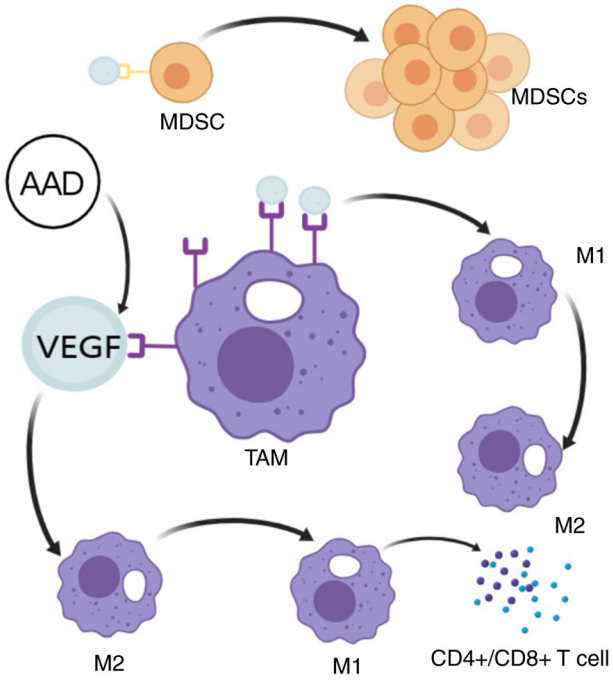

Figure 2. Anti-angiogenesis therapy can improve immunosuppression in the tumour microenvironment. AAD, anti-angiogenesis drug; MDSC, myeloid-derived suppressor cell; TAM, tumour-associated macrophage.

exert synergistic antitumour effects when combined with IT drugs (90). Furthermore, the expression of VEGFR is regulated by hypoxia in a hypoxia-inducible factor (HIF)-dependent manner, while the stable expression of HIF-1α was demonstrated to be dependent on ROS production, indicating ROS regulates the expression of VEGFR (91). Under hypoxic conditions, VEGFR expression in TAMs is increased, and TAMs bind more VEGF, activate the PI3K/AKT signalling pathway, inhibit proinflammatory M1 polarisation and promote the expression of anti-inflammatory and repair-associated M-type markers (92).

On the other hand, VEGFR-activated tumour cells secrete factors including IL-10 and TGF-β, which directly induce the transformation of macrophages into the M2 type. Several mechanisms work together to promote the transformation of TAMs from M1 to M2, enhance immunity and angiogenesis and promote tumour development (93). Therefore, anti-VEGF therapy normalises blood vessels, improves hypoxia, reduces VEGFR expression and converts TAMs from immunosuppressive M2 cells to immune-stimulating M1 cells through multiple mechanisms (92). M1 cells can produce large amounts of ROS and nitric oxide, which can directly induce DNA damage and apoptosis in tumour cells. Furthermore, IL-12 and IL-18 are secreted to inhibit VEGF expression, block tumour angiogenesis and serve a tumour suppressor role (94). In addition, M1-type macrophages can present tumour antigens to $CD4^+$ T cells, recruit $CD8^+$ T cells to the tumour site and mediate the ability of IL-12 to increase their killing activity and promote $CD4^+$ and $CD8^+$ T-lymphocyte infiltration, thereby improving the tumour immunosuppressive microenvironment (95).

Enhancing IT and reversing immune resistance are important for AAT combined with IT to achieve notable antitumour effects. The addition of bevacizumab to atezolizumab

produced sustained biochemical and radiographic responses that appeared to overcome resistance to nivolumab monotherapy (96). Anlotinib can regulate the tumour immunosuppressive microenvironment and may help reverse ITR (12,13). Apatinib can alleviate high angiogenesis and hypoxia in the microenvironment, improve immunosuppressive agent efficiency in tumours with VEGFA overexpression and overcome innate resistance to immunosuppressive agents in tumour models with high angiogenesis (97). An increasing number of clinical studies support that combined AAT and IT can improve ITR and improve the prognosis of malignant tumours (98-100).

5. Immunosuppressants

IT and immune resistance. In tumour tissues, cancer cells, immune cells and other stromal cells interact to generate an immunosuppressive microenvironment through a variety of immunosuppressive factors, such as interleukin-10 and hyaluronic acid (101). Therefore, PD-1/PD-L1 has become the main target of IT (102). With immunosuppressant development, IT has been recommended as the first-line treatment for patients with NSCLC. However, certain patients are considered resistant to IT during treatment, and the mechanism of ITR is still being explored (103). Contemporary ideas point to a variety of factors that may contribute to immune resistance. Regardless of genomic, immune system, cancer microenvironment-associated or host cell-generated factors, ITR can emerge during treatment and lead to treatment failure (104-106). Various combined therapies, such as immunotherapy combined with radiotherapy, have prevented and reversed immunosuppressant resistance to a certain extent (107-109). The study by Abou Khouzam *et al* (110) proposed that hypoxia induces angiogenesis and subsequent immunosuppression, which is the main reason for IT failure. The study by Larroquette *et al* (111) proposed that combining chemotherapy and IT can disrupt the ITR of the NSCLC TME. However, chemotherapy is not well tolerated in patients with NSCLC with BMs, and it is thus important to develop other methods.

Immunosuppressive agents affect the microenvironment of BMs. Due to differences in the TIM, the response of primary tumour lesions and BMs to the IT of NSCLC may be inconsistent (112). The antitumour $CD8^+$ T cells are relatively deficient in intracranial tumours and there are more dysfunctional $CD8^+$ T cells compared with primary tumours. Furthermore, intracranial macrophages and dendritic cells have increased protumour and anti-inflammatory effects (113). Additionally, PD-1 tumour-infiltrating lymphocytes are less permeable in BMs, which may markedly reduce the ICI effect of anti-PD-1 therapy. However, PD-L1 expression is usually higher in metastatic sites compared with primary tumours, which is also associated with the efficacy of ICIs (114). Studies have demonstrated that PD-1/PD-L1 expression can be employed as an independent predictor of survival in patients with NSCLC with BMs who receive IT (19,114). When BMs develop from NSCLC, PD-1 is expressed on activated T cells, monocytes and dendritic cells, and PD-L1 is also expressed on tumour and immune cells in the brain. In this immune microenvironment, PD-1/PD-L1 inhibitors may have a notable antitumour effect on BM (115,116). Therefore, for patients with NSCLC with BMs, the use of immunosuppressive agents can achieve improved efficacy.

Combined IT improves treatment efficacy in patients with NSCLC with BMs. IT is an effective treatment for a variety of advanced cancers and the IT combined with targeted therapy, chemotherapy, or radiotherapy is the standard first-line treatment for patients with advanced NSCLC with negative driver genes (117,118). The results of a study by Yu *et al* (119) showed that patients with lung cancer with liver metastases derive less benefit from IT compared with patients with BMs. Therefore, patients with BMs have an improved basis for organ-specific IT. In a meta-analysis published in 2023, the authors investigated the potential benefit of different treatment options for intracranial lesions in patients with NSCLC that is negative for driver genes (120). The results showed that immunosuppressant-based combination therapy provided a long-term survival benefit for patients receiving non-targeted therapy compared with patients who did not receive immunotherapy. The results of another meta-analysis also showed that IT was effective in patients with non-targeted NSCLC (121). Therefore, IT serves an important role in cancer treatment, and combination therapy can delay disease progression and prolong patient survival to a certain extent (122,123).

IT combined with RT provides the best local control for patients with BM without increasing the risk of toxicity (124). A multicentre retrospective study by the Italian Society of Radiotherapy and Clinical Oncology reached similar conclusions (125). Additional studies have also reported that using ICIs combined with RT improves OS and reduces the risk of brain failure and neurological mortality in patients with NSCLC with BMs compared with a single treatment (126-128). ICIs have effective radiosensitizing effects and can synergistically enhance antitumour effects in combination with brain RT (129,130). Furthermore, since AAD promotes antitumour immune responses (131,132), the combination of IT and AAT may notably impact the BMs (133). Other studies have demonstrated increased anticancer efficacy after adding AAT to immunosuppressive agents (134,135). IT combined with AAT can markedly improve the OS of patients with NSCLC driver gene mutation-negative BMs (136). In conclusion, ICIs combined with AAT and RT may have notable survival benefits for patients with NSCLC.

6. Triple-injection therapy can increase treatment efficacy and reverse immune resistance

Previous studies have demonstrated that IT combined with RT, IT combined with AAT and RT combined with AAT achieve notable clinical benefits in the treatment of patients with NSCLC with BMs, and no serious grade 4-5 adverse reactions were reported in the process of combined treatment (137-141). However, no clinical trials have investigated the combination of these three treatments in patients with NSCLC with BMs. On the one hand, there is no clear indication for the combination therapy with these three treatments and most clinicians use combination therapy with two treatments (142,143). On the other hand, although there are safety reports on combination therapy, these reports are rare, and

most are basic experiments and have not been translated into clinical practice. For example, combination therapy with aspirin, afatinib and vinorelbine was significantly more effective than monotherapy in NSCLC cell models (144,145). As a result, research into the simultaneous application of multiple treatments has been hindered.

AAT, IT and RT can affect the intracranial immune microenvironment of patients with BMs and exert antitumour effects. However, it currently remains elusive whether the simultaneous use of these three methods will synergistically change the TME and achieve stronger antitumour effects. To date, numerous studies have investigated the mechanism of AAT combined with IT and demonstrated that the combined therapies can have a stronger antitumour effect (146,147). However, relatively few studies have investigated the combination with RT. In animal experiments, RT combined with anti-PD-L1 and anlotinib therapy increased the number of tumour-infiltrating lymphocytes and reversed the immunosuppressive effect of RT on the TIM. These findings suggest that AAT may be a potential radioimmunotherapy synergistic therapy to achieve improved antitumour efficacy in patients with NSCLC by enhancing the TIM (148,149).

Previous mechanistic studies have shown that AAT promotes vascular normalisation and immune cell infiltration, RT provides antigen release and *in situ* vaccine effects and IT maintains T-cell activity, thereby forming a beneficial cycle (42,150). The molecular mechanisms by which these three factors regulate the TIM through multiple dimensions include the following: First, AAT serves a central role by targeting VEGF/VEGFR and other pathways to reduce tumour vessel density, inhibit abnormal angiogenesis, alleviate hypoxia, improve vascular permeability and promote T-cell penetration and drug delivery (89,151). Second, IT enhances antitumour efficacy by restoring T-cell function and promoting the antitumour immune response while synergistically activating T cells in combination with RT (89,152). Finally, RT can upregulate PD-L1 expression and enhance immune recognition while providing an antigen 'immune' effect, maintaining a long-term response to IT and increasing the anti-angiogenic therapeutic window (153). The combination of these three treatments not only reverses 'immune-excluded tumours' to 'immune-inflamed tumours' in the presence or absence of a strong immune response within the TME to enhance the antitumour effect but also alleviates single-drug resistance, providing long-term benefits for the treatment of advanced tumours (150).

The molecular mechanisms of RT in combination with IT and AAT for malignant tumour treatment are described in Fig. 3. RT irradiation leads to tumour cell death and the recruitment of numerous cytokines, chemokines and growth factors in the TME. In addition, RT causes the recruitment of immune cells while activating tumour antigen-presenting dendritic cells through the apoptosis of immunogenic tumour cells, the activation of innate immunity and the activation of cytotoxic T lymphocytes (CTLs). This antigenic 'vaccine' effect provided by RT could allow anti-PD-1 agents to further enhance CTL activation, induce immune memory and amplify systemic antitumour responses through an 'abnormal effect'. AAT can inhibit abnormal angiogenesis, improve vascular structure and function in the short term and restore the blood

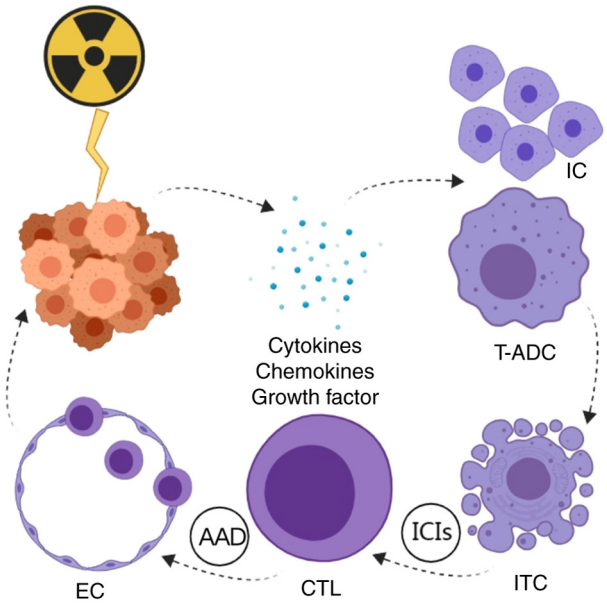

Figure 3. Mechanisms of radiotherapy combined with immunotherapy and anti-angiogenesis therapy in the treatment of malignant tumours. IC, immune cells; T-ADC, tumour antigen-presenting dendritic cells; ITC, immunogenic tumour cells; ICIs, immune checkpoint inhibitors; CTL, cytotoxic T lymphocytes; AAD, anti-angiogenesis drug; EC, endothelial cells.

vessels to normal. PD-1 IT releases interferon, which allows CTLs to have an antitumour effect through endothelial cells in structurally normalised blood vessels and cooperate with RT and IT (42,52).

The meta-analysis performed by Xian *et al* (154) demonstrated that in the treatment of solid tumours, ICIs combined with RT and AAT showed improved survival benefits compared with single or dual drug combination therapy, and triple therapy was tolerable and safe. However, the analysis did not identify specific cancer conditions to evaluate tolerability, and the safety of triple therapy in patients with NSCLC BMs has not been evaluated in the published literature. Therefore, all patients in Table I screened for NSCLC BMs were treated with double therapy, and the safety evaluation was acceptable. The main adverse reactions included leukopenia and other haematological toxicities, such as hypertension. The incidence of radiation-induced brain necrosis was not high, possibly because AADs increase vascular permeability, which not only improves brain oedema during RT but also reduces the occurrence of radiation-induced brain necrosis. However, AADs can markedly increase blood pressure. In clinical practice, certain patients cannot use these drugs due to difficulty in blood pressure control (155). For these patients, the dose should be reduced or used cautiously. In addition, no obvious immune-related adverse events occurred in patients receiving the two-combination therapy. The 2023 case report by Long *et al* (156) described a 55-year-old patient with BMs from advanced small-cell lung cancer who received combined treatment consisting of anlotinib and WBRT, with anti-PD-L1 IT in combination with anlotinib as long-term maintenance therapy. The OS was 41 months after the onset of BM and no serious adverse reactions occurred. The application of IR and TT has improved BM treatment and several studies have suggested that IT or TT is effective for patients with NSCLC

Table I. Clinical trials evaluating the efficacy and safety of combination therapy for patients with non-small cell lung cancer with brain metastases.

Author, year	Study type	Treatment strategies	Dosage of drugs	Patients, n	OS or PFS	ORR or DCR	Major adverse events	Dose titration	Safety	(Refs.)
Xian *et al*, 2024	Systematic review and meta-analysis	PD1/PDL1 inhibitors, AAT, RT	NA	365	NA	ORR, 48%; DCR, 92%	Leukopenia (25%), thrombocytopenia (23.8%), fatigue (23.2%), gastrointestinal discomfort (22%), increased alanine aminotransferase (22%) and neutropenia (21.4%)	NA	Combination therapy is tolerable and safe	(154)
Chen *et al*, 2022	Clinical trial	Rh-endostatin, WBRT	Rh-endostatin 30 mg/day	19	OS, 14.2 months; PFS, 11.6 months	ORR, 52.6%; DCR, 84.2%	NA	NA	Improved local blood supply and micro-circulation	(192)
Yang *et al*, 2017	Clinical trial	Bevacizumab, gefitinib, WBRT	Bevacizumab 5 mg/kg	76	OS rate, 48.6%; PFS rate, 29.8%	ORR, 80.3%; DCR, 96.1%	Rash (75.0%), hypertension (56.6%), proteinuria (43.4%)	Yes	No patients developed grade ≥4 AEs	(193)
Xu *et al*, 2025	Clinical trial	SRS/WBRT, camrelizumab, doublet chemotherapy	Camrelizumab 200 mg Q3W	65	DFS, 71.7%	NA	Neutrophil count (22%), decreased white blood cell count (15%), decreased platelet count (15%), decreased lymphocyte count (14%), neurological toxic (5%), radiation necrosis (5%)	NA	Manageable toxicity	(194)
Enright *et al*, 2021	Clinical trial	SRS, ICI	NA	33	Improved OS	NA	Neurologic death, distant brain failure	NA	Distant brain failure and risk of neurologic death are decreased	(127)
Song *et al*, 2023	Clinical trial	PD-1 inhibitors combined, AAT	NA	62	OS, 21.4 months	Compared with single drug, DCR was notable	NA	NA	Compared with single drug, AE incidence was not statistically significant	(136)

RT, radiotherapy; SRS, stereoscopic radiosurgery; SRT; stereoscopic body radiation therapy; AAT, anti-angiogenic therapy; ICI, immune checkpoint inhibitors; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1; WBRT, whole brain radiotherapy; ORR, objective response rate; PFS, progression-free survival; OS, overall survival; DCR, disease control rate; AE, adverse events; DFS, disease-free survival.

with BMs (102,157). Therefore, combining the three therapies may have clinical benefits in the treatment of patients with NSCLC with BMs with no serious adverse reactions.

The results of previously published meta-analyses indicate that most studies on AAT combined with IT and RT consist primarily of animal trials, retrospective analyses, a limited number of case reports and single-arm trials with small sample sizes (154,158). These studies demonstrate that triple therapy can enhance the efficacy of antitumour treatment without inducing severe adverse reactions. To date, IT plus chemotherapy combined with AAT has achieved good results in a number of randomized controlled trials (159,160), and the results of certain clinical trials have demonstrated that RT plus chemotherapy combined with IT or AAT has effective antitumour treatment effects (161,162). However, there is still a lack of large clinical randomized controlled trials of RT combined with IT and AAT. Results of a phase II trial indicated that triple therapy plus chemotherapy showed promising antitumor activity and was well tolerated in advanced solid tumours (163). Therefore, further investigation is warranted into the integration of AAT with RT and IT (164,165). The present article provides an in-depth feasibility analysis of triple therapy for patients with NSCLC with BMs, concluding that such therapy improves patient survival with controllable safety. Based on these findings, a clinical observation project has been initiated for triple therapy in patients with NSCLC with BMs. The project has received ethical approval and is currently recruiting participants, aiming to encourage more institutions to perform large-scale clinical trials, which represents one of the key directions for future research.

WBRT is currently the first choice for patients with NSCLC with extensive BMs. SRS alone can be performed for patients with 1-4 metastatic lesions, SR can be provided after craniocerebral surgery for patients with 1-2 metastatic lesions and WBRT + SRS can be performed for patients with numerous metastatic lesions but no extensive metastases (5). A previous study demonstrated that patients receiving WBRT + SRS or SRS alone have similar intracranial control rates and survival benefits; however, patients receiving WBRT + SRS have more severe cognitive impairment (166). Therefore, regardless of the number of BMs, different RT methods can result in similar therapeutic responses, but when combined with systemic therapy, RT needs to be selected. For triple therapy, patients who can undergo SRS are more inclined to be selected to reduce adverse reactions. The application of local therapy is suitable for most patients with NSCLC with BMs, and their treatment response mainly differs with respect to the choice of systemic therapy (167).

According to the current clinical guidelines, targeted therapy is the first choice of systemic therapy for patients with NSCLC with BMs and positive driver genes (5). However, due to the blood-brain barrier, there is no strong evidence-based foundation for the systemic treatment of patients with negative driver genes (5). The results from the phase III IMpower150 study (168) revealed statistically and clinically notable PRS with combination therapy regardless of PD-L1 expression or EGFR or anaplastic lymphoma kinase mutation status. However, in patients with positive driver genes, targeted therapy seems to achieve improved survival benefits compared with patients without driver genes (168). Sintilimab plus anlotinib showed durable efficacy in metastatic NSCLC with rare EGFR mutations in a phase II study (169). Similarly, in another study, benmelstobart combined with anlotinib showed promising antitumor efficacy and a tolerable safety profile in patients with EGFR-positive advanced NSCLC after the failure of EGFR TKI (170).

As previously discussed, AAT can reverse immune resistance and exert more powerful antitumour effects in combination with IT. Therefore, it is important to evaluate the factors affecting IT and AAT efficacy. Tumours with high expression of PD-L1 (such as NSCLC) may be more sensitive to PD-1/PD-L1 inhibitors, and certain PD-L1-negative patients may still benefit. Therefore, the population suitable for IT may be selected by detecting PD-L1 expression in clinical practice. By selecting patients with a tumor proportion score (TPS) ≥1%, partially negative patients can also be evaluated for IT. In addition, different drugs can be selected based on the TPS value for more precise IT (171). The VEGF expression level can affect AAT efficacy; tumours with high VEGF expression may be more sensitive to AAT, but certain tumours with low VEGF expression may also be responsive. Serum/plasma VEGF levels can be used to predict treatment efficacy, and high VEGF levels may have greater effects on patients (172). However, it is necessary to carefully select anti-VEGF drugs for patients with hypertension and closely observe blood pressure changes during their use as hypertension is the most common adverse reaction to anti-VEGF drugs (172). Therefore, triple therapy is mainly used in patients with negative driver genes but can also be used in patients with positive driver genes where targeted therapy failed.

In addition, due to the increased risk of life-threatening radiation necrosis and oedema in the brainstem and cerebellum after RT, the treatment strategy should be carefully considered in triple therapy, including the RT dose, AADs, IT drug dose and duration (173,174). For BMs, both functional and non-functional areas should be considered in RT. The performance of RT in functional areas is similar to that in the brainstem, and the combination of AADs can effectively relieve oedema and reduce the side effects of RT to a certain extent, while there is no limitation in non-functional areas (175). However, the treatment effect and survival of patients with leptomeningeal metastasis are poor, and these patients are not sensitive to palliative RT. Combined therapy may increase the burden on patients, and accordingly, triple therapy is not recommended (176).

Since the approval of IT for NSCLC treatment, patients treated with ICIs have obtained notable survival benefits compared with previous treatments (177,178). To date, with the continuous application of IT, numerous patients have developed ITR, which severely affects disease treatments (179,180). Exploring the mechanisms of resistance to immunosuppressants is crucial for further improving their clinical benefit (181). A variety of IT combination therapies have prevented and reversed ITR (182,183). Currently, an increasing number of clinical trials are exploring the safety and efficacy of combination therapy in patients with NSCLC with ICI resistance (183,184). AAT, RT, IT and other treatments will affect the TIM, which may reverse ITR and improve clinical efficacy (153,185,186). However, previous studies choose two of the three treatment methods: RT, IT and TT for combined treatment and their efficacy achieved satisfactory results with relatively few side effects (187-189). However, as the disease progressed, the two treatments were

not sufficient, so triple therapy was explored. The results from animal experiments demonstrate that triple therapy can notably delay tumour growth and enhance the survival rate compared with two or single treatments (148,190), which is expected to be further extended to clinical application and bring new survival benefits.

Triple therapy is currently being explored in animal models; however, only one study has been published to date (148). Although the effect of triple therapy in animal models is notable, these models still have certain limitations. First, the survival observation time and the establishment form of the animal model were insufficient, and the effect of triple therapy on survival and tumour recurrence has not been observed in the experimental process. Second, there are no animal models to investigate whether different RT dose fractionations affect the efficacy of triple therapy. Finally, the effects of RT and different dosing intervals on efficacy have not been explored. There remains a need to study triple-therapy animal models in the future. However, owing to the notable differences in gene number, expression profile and ligand binding and function between human and murine TIM proteins, the same therapeutic strategy that works well in animal models may not work well in humans (191-194). Therefore, phase II or III clinical trials should be performed under ethical conditions to assess the efficacy and safety of triple therapy. This will not only provide new treatment strategies for patients with advanced NSCLC with BMs but also provide new ideas for the treatment of other cancers.

There are still numerous directions for future research. First, based on the evidence discussed in the present review, triple therapy can achieve good efficacy and controllable safety in patients with NSCLC with BMs, but there is a lack of large-scale prospective clinical trials to verify this; therefore, further studies are needed to evaluate its clinical benefits. Second, triple therapy can be used in the treatment of other cancers, such as liver cancer or pancreatic cancer, to provide new ideas for tumour inhibition, but this also needs to be evaluated by clinical trials. Third, the mechanism by which triple therapy jointly regulates the TIM is not fully understood and changes in the TIM when the three treatments are used simultaneously need to be explored further. Finally, at present, most studies on TIM regulation by triple therapy are carried out in animal models; therefore, future studies using human tissues or blood are needed. This article also has certain limitations. There are relatively few relevant studies including triple therapy and there is a lack of prospective clinical trials to prove its effectiveness. Secondly, it only provides a new treatment idea for patients with NSCLC with BMs and does not extend to include more methods. This is expected to be addressed in future studies.

7. Conclusions

RT combined with AAT and IT has a synergistic effect in the treatment of patients with BMs from NSCLC and may reverse the ITR during treatment. Combination therapy may provide additional survival benefits to patients with NSCLC with BMs, but its specific efficacy and safety need to be explored further.

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Authors' contributions

ML was involved in the conceptualization, validation, formal analysis, investigation, data curation and writing the original draft. JG was involved in formal analysis, investigation, and manuscript review and editing. FL was involved in formal analysis, visualization and methodology. CG was involved in visualisation and methodology. JZ was involved in conceptualization and formal analysis. LW was involved in project administration, conceptualisation, manuscript review and editing, and resources/funding acquisition. YX was involved in resources, project administration, conceptualisation, project administration, manuscript review and editing, and funding acquisition. Data authentication is not applicable. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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