OncoTargets and Therapy

Dovepress
Taylor & Francis Group

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REVIEW

Roles of SPOCK1 in the Formation Mechanisms and Treatment of Non-Small-Cell Lung Cancer and Brain Metastases from Lung Cancer

Xuebing Zhang[1,*], Xia Zhang[1,2,*], Hang Yin[1], Qizheng Li[1], Buqun Fan[1], Bolun Jiang[1], Anqi Xie[1], Dandan Guo[1], Huanling Hao[3], Bin Zhang[1]

[1]Department of Oncology, The First Affiliated Hospital of Dalian Medical University, Dalian, Liaoning, People's Republic of China; [2]Department of Oncology, Dalian Fifth People's Hospital, Dalian, Liaoning, People's Republic of China; [3]Department of Oncology, Dandong First Hospital, Dandong, Liaoning, People's Republic of China

*These authors contributed equally to this work

Correspondence: Bin Zhang; Huanling Hao, Email Zhangbin_dlmu@163.com; 112308162@qq.com

Abstract: Lung cancer is a malignant tumor with high morbidity and mortality in China and worldwide. Once it metastasizes to the brain, its prognosis is very poor. Brain metastases are found in about 20% of newly diagnosed non-small-cell lung cancer (NSCLC) patients. About 30% of NSCLC patients develop brain metastases during treatment. NSCLC that is positive for EGFR, ALK, and ROS1 variations is especially likely to metastasize to the brain. SPOCK1 is a proteoglycan with systemic physiological functions. It regulates the self-renewal of brain metastasis–initiating cells, regulates invasion and metastasis from the lung to the brain, plays an important role in tumor progression and treatment resistance, and has higher expression in metastatic tumor tissues than other tissues. Current treatments for NSCLC brain metastases include surgery, whole-brain radiotherapy, stereotactic radiotherapy, targeted therapy, and chemotherapy. SPOCK1 is involved in many signaling pathways, by which it influences a variety of NSCLC treatment methods. In this paper, the progress of research on the treatment of NSCLC brain metastases is reviewed to guide decisions on treatment options in clinical practice.

Keywords: SPOCK1, non—small cell lung cancer, NSCLC, brain metastasis, chemotherapy, targeted therapy, immunotherapy

Introduction

Lung cancer is one of the malignant tumors with the highest morbidity and mortality in China and worldwide. Once lung cancer metastasizes to the brain, the disease progresses to an advanced stage.[1] One study discussed the molecular epidemiology of the main druggable genetic alterations in NSCLC, ie, mutation or amplification of EGFR, KRAS, BRAF, MET, and HER2, as well as fusions of ALK and ROS1, and their roles in the incidence of brain metastases.[2] ROS1 is rearranged in 0.9–2.6% of NSCLC patients. Several gene fusion partners of ROS1 have been identified, the most common being CD74, and brain metastases are diagnosed in up to 36% of patients with ROS1 fusion–positive NSCLC at the time of diagnosis.[3] ALK rearrangement occurs in only 4.5% of NSCLC patients, almost all of them adenocarcinoma patients. It is more common in young nonsmokers and women, and its presence is conducive to brain metastasis. At the time of NSCLC diagnosis, 20% of patients with ALK gene rearrangement have brain metastases, and 40–50% of these patients develop central nervous system (CNS) metastasis during the course of the disease. The blood–brain barrier (BBB) limits the efficacy of chemotherapy for CNS metastasis, while the efficacy of targeted therapy varies significantly by its ability to cross the BBB.[4] For patients with brain metastases who gain limited benefit from targeted therapy, radiotherapy is the main treatment in addition to surgery. Brain radiotherapy can significantly damage the integrity of the BBB. The selection of the radiotherapy regimen for NSCLC brain metastases is particularly important. Stereotactic radiosurgery (SRS) and whole brain radiotherapy (WBRT) differ in important ways. For instance, the

Received: 12 August 2024
Accepted: 9 December 2024
Published: 16 January 2025

changes in cognitive function caused by WBRT have been criticized by some doctors. It is certain that the combination of RT and molecular-targeted therapy has greatly improved patient survival.

Tumors can invade the CNS by multiple mechanisms, including loss of adhesion to cells, interaction with the tumor microenvironment, cytokine activation, and microRNA action.[5]

Hu Ling et al determined the in vitro metastasis-associated behavior of a highly brain-metastatic subclonal cell line, PC14 /B, compared with primary PC14 cells and A549 cells that did not metastasize to the brain. The expressions of vascular epithelial growth factor (VEGF), matrix metalloproteinase 9 (MMP-9), S100B and epidermal growth factor receptor (EGFR) in the above three cell lines were detected by immunohistochemical staining and Western blot. It was found that the expression levels of VEGF and MMP-9 in PC14/B cells were much higher than those in PC14 and A549 cells. Compared with those in other tumors, the MMP-9 level is increased in brain metastases from lung cancer.[6] Compared with patients without brain metastases, patients with brain metastases have higher levels of CXCL12 and its receptor CXCR4, indicating that the former phenotype is more prone to cell migration.[7] Several growth factor pathways and their receptors with protein kinase activity are also associated with the development of brain metastases. EGFR and ERK expression is increased in brain tumors. In lung cancer, the expression of proteins in this pathway has even been found to be greater in metastatic tumors than in primary tumors. VEGF expression is increased in NSCLC patients with brain metastases. Research on brain metastasis mechanisms are ongoing. Investigators at McMaster University have obtained brain metastatic tissue from non-small-cell lung cancer patients with brain metastases and used specific cell culture methods to enrich a population of tumor cells with features of cancer stem cells. The researchers injected the rapidly dividing and migrating population of tumor cells, called brain metastasis initiating cells (BMICs), into the brain, lungs and circulation of mice, They discovered that BMIC cells injected into the blood circulation were directed to form metastases in brain tissue but fail to generate tumors in the lungs. BMIC cells injected into the lungs can form tumors in the lungs and also in the brain through the blood circulation. The investigators screened BMICs cells from the ShRNA gene bank and found that ShRNA targeting TWIST2 and SPOCK1 caused the most significant reduction in BMIC cell migration and proliferation in vitro. In vivo experiments, they knocked down TWIST2 or SPOCK1 expression in BMIC cells, and when these cells were injected into mice, they found that the ability of these cells to generate brain metastases in the brain was significantly reduced. This study revealed the important roles of SPOCK1 and TWIST2 in brain metastasis,[8] especially SPOCK1. This paper reviews the evidence on the role of SPOCK1 in NSCLC, hoping to provide ideas for clinical research.

The Effect of SPOCK1 on Tumor Invasion and Metastasis

SPOCK1, also known as testican-1, is a modular proteoglycan. Its gene spans at least 70 kb and consists of 11 exons. This gene is located between the IL9 and EGR1 genes and borders the smallest commonly deleted region on chromosome 5.[9] SPOCK1 is abundantly expressed in the brain, especially in the thalamus, followed by prostate, testes, heart, blood, and cartilage tissues.[10] As a conserved multidomain proteoglycan, SPOCK1 has many biological functions, such as extracellular matrix (ECM) remodeling and the regulation of neuronal function. SPOCK1 expression is significantly increased in some tumors, such as lung cancer, liver cancer, renal cancer, prostate cancer, and colorectal cancer,[11–13] and is significantly correlated with tumor metastasis. The expression of SPOCK1 is increased in stroke, when a large number of astrocytes are activated. SPOCK1 may be involved in brain tissue remodeling and axonal regeneration. SPOCK1 inhibits the attachment of Neuro-2a cells and promotes the neurite outgrowth of neurons. Its mutation also leads to developmental delay and mental retardation in children and may be one of the causes of cancer metastasis to the brain.[14] SPOCK1 alters the homeostasis of the ECM, which in turn triggers metastasis, as ECM and basement membrane degradation play key roles in tumor metastasis and invasion. SPOCK1 is classified as a regulator of the ECM and can interact with the cell surface. SPOCK1 can both protect against and promote tumor cell invasion and metastasis.[15]

Mechanism by Which SPOCK1 Affects Invasion and Metastasis

A unique region located after the N-terminal region of SPOCK1 inhibits the activity of certain matrix metalloproteases, such as MT1-MMP. MT1-MMP is involved in ECM degradation and remodeling and intracellular signal transduction and mediates tumor invasion and spread. It has been observed that the mRNA and protein of MMPs −1, −2, −3, −7, −8, −9, −13

and MT1-MMP are overexpressed in CNS tumor cells. Yu et al evaluated the effect of SPOCK1 on proliferation, migration and invasion of glioma cells.[16] They observed The level of MMPs is positively correlated with the invasiveness of glioma cells. SPOCK1 overexpression can stimulate the expression and activity of MMP-9 and MMP-2 (MMP-9 plays an important role in tumor metastasis and invasion), thus shrinking the ECM and promoting the invasion of glioma cells. The increased expression of molecules such as metalloproteases (MMP2-MMP9) and VEGF induces disruption of the BBB (especially the tight junctions of the endothelium) and enhances the infiltration of tumor cells. Many scholars speculate that in glioblastoma patients, due to this infiltration, the BBB no longer restricts drug delivery, so the efficacy of glioblastoma treatment is no longer limited.[17] It can be speculated that such infiltration would have a similar effect in brain metastases.

Relationship Between SPOCK1 and the BBB

Relationship with the BBB: Researchers at Harvard Medical School found that neurons activate SPOCK1 signaling to promote BBB formation and maintain its protective properties, revealed the extent of SPOCK1 signaling into the vascular system, and identified the mechanism by which SPOCK1 signaling controls endothelial cell phagocytosis through the control of the pericyte endothelial ECM.[18] The BBB provides a homeostatic environment that strictly limits the brain's permeability to proteins and small molecules and is essential for the maintenance of normal neuronal function. The BBB also prevents drugs from entering the brain at more than trace levels. If we understand how to regulate the permeability of the BBB, the BBB can be temporarily opened to allow chemotherapy pathways to attack brain tumors, greatly increasing the efficacy of chemotherapeutic drugs. The SPOCK1 protein produced by neurons enters the BBB, initiates proper formation of the barrier during embryonic development, and helps maintain the barrier thereafter. SPOCK1 is a powerful secreted neural signal that promotes and induces barrier properties in these blood vessels, and the BBB would not function without it.[19]

Effects of SPOCK1 on Lung Cancer and Its Metastatic Pathways

SPOCK1 is expressed significantly higher in lung cancer tissues and metastatic tissues than paracancerous tissues. In epithelial lung cancer cells, SPOCK1, as a transforming growth factor (TGF)-β target gene, can regulate the EMT process in lung cancer cells. In some lung adenocarcinomas, the expression of mutated TGF-β ligands is reduced in brain metastasis-initiating cells with *SPOCK1* knockdown. TGF-β ligands promote tumor progression, mediate cancer cell migration and metastasis, and induce the transformation of some epithelial cells into mesenchymal cells.[20] Wang et al reported that silencing of SPOCK1 in lung cancer cells could inhibit the activation of the Wnt/β-catenin pathway, significantly reducing the proliferation, migration, and invasion abilities of lung cancer cells, and that targeting SPOCK1 may be a new strategy for the treatment of lung cancer.[21] Liu et al found that overexpression of SPOCK1 could drive EMT and induce immune escape of tumor cells, resulting in poor survival outcomes, suggesting that SPOCK1 might be a potential therapeutic target for clinical lung adenocarcinoma.

SPOCK1 expression is upregulated in lung adenocarcinoma tissues, and its expression is associated with poor prognosis. In one study, patients in the high-SPOCK1 group exhibited more activation of malignant oncogenic pathways, higher infiltration of immunosuppressive components, and higher mutation frequency. Knockdown of SPOCK1 suppresses the invasion and metastasis ability of lung adenocarcinoma cells, and high expression of SPOCK1 is associated with low infiltration of $CD8^+$ T cells.[20] SPOCK1 is significantly overexpressed in osimertinib-resistant lung cancer cells. The deletion of SPOCK1 inhibits the proliferation of osimertinib-resistant cells and sensitizes drug-resistant cells to osimertinib, indicating that SPOCK1 plays a positive regulatory role in osimertinib resistance and may become a new therapeutic target.

Importantly, the upregulation of SPOCK1 promotes tumor invasion and metastasis and shortens survival time, contributing to a poor prognosis in cancer patients.[22] Riti Roy et al conducted correlation analysis between target drugs and gene level expression and found that almost half of the drugs had two or more targets. Researchers detected the number of genes with better correlation between non-target and drug sensitivity than target, and summarized the ranking of target genes. In the future, the correlation analysis between target drugs and SPOCK1 gene expression can be performed to find out relatively sensitive drugs to treat NSCLC BM patients".[23]

 https://doi.org/10.2147/OTT.S483576

In conclusion, SPOCK1 may be an independent prognostic factor for NSCLC and a candidate therapeutic target for osimertinib-resistant lung tumors. In recent years, it has been shown that various signaling pathways of SPOCK1 gene are involved in the occurrence and progression of tumors, and its function of inhibiting tumor cell apoptosis and promoting tumor invasion and metastasis has received much attention.

Current Treatment Methods for Lung Cancer Brain Metastases and the Functional Mechanism of SPOCK1 in Treatment

Local Treatment

Surgery

Surgical resection is suitable for patients with only 1–3 tumor lesions that are greater than 3 cm in diameter, located in superficial and nonessential functional areas, where the tumor or its edema occupies a large space or causes hydrocephalus. In principle, surgery is not the first choice for brain metastases located in the brainstem, thalamus, or basal ganglia. For patients with solitary brain metastasis from lung cancer with well-controlled extracranial lesions and good performance status, surgical resection or SRS is recommended as a local treatment; WBRT is thought to be useful for multiple CNS metastases.[24] The combination of neurosurgical resection and postoperative RT is beneficial for the treatment of solitary brain metastases. Surgery combined with chemotherapy or RT achieves better results than surgery alone.

Radiotherapy

A recent study showed that in patients with brain metastases, RT for brain metastases resulted in better local control than targeted therapy.[25]

Prophylactic brain RT: Percutaneous coronary intervention is an effective option for patients with limited SCLC. It improves overall survival and progression-free survival and delays and reduces the incidence of brain metastases without a significant effect on survival.[26]

WBRT: WBRT is indicated as the salvage therapy after SRS failure, as the initial treatment for patients with NSCLC brain metastases with more than three lesions, as adjuvant therapy after resection of intracranial lesions, and for patients with extensive-stage small-cell lung cancer with brain metastases. Compared with SRS, WBRT can better open drug-delivery barriers in the CNS, thereby making it more effective in combination with drugs. In the context of systemic drug therapy, WBRT+simultaneous integrated boost may lead to better intracranial local control than SRS in NSCLC brain metastasis patients.[27] In addition, as the survival time of patients with brain metastases from lung cancer increases, we need to be aware that the neurocognitive impairment caused by WBRT is mainly related to the hippocampus. A trial showed that cranial RT with hippocampal avoidance (HA-CRT) (conventional RT) seems to be safe for lung cancer patients, but it may not be superior to CRT. It is necessary to conduct larger randomized controlled trials comparing HA-CRT and CRT.[28]

SRT: SRS consisting of a single fraction or SRT consisting of 2–5 fractions is supported. SRS has the advantages of precise positioning, concentrated dosage, and relatively little damage, and it can effectively protect surrounding normal tissues, control the progression of local tumors, and relieve neurological symptoms while having minimal impact on neurocognitive function. Therefore, it has gradually become an important option for treating brain metastases. For patients with driver gene mutation–positive NSCLC without metastasis to other sites, who cannot undergo resection and/or who have a limited number of brain metastases (1–4), SRS alone can better preserve cognitive function and has become their preferred treatment.[29] With 5–10 brain metastases, brain SRT or WBRT is recommended. Most scholars believe that SRS can better protect the cognitive function of patients than can WBRT. A retrospective cohort study of EGFR tyrosine kinase inhibitors (TKIs) combined with RT for the treatment of non-small-cell brain metastases conducted by Tatineni et al showed that NSCLC brain metastasis patients receiving SRS had significantly longer overall survival than patients treated with WBRT only.[30] In the study by Xu et al, it was discovered that NSCLC cells with T790M mutation gefitinib resistance (PC-9-GR) exhibited higher radiosensitivity compared to NSCLC cells without the mutation, potentially mediated by SPOCK1: RNA sequencing revealed down-regulation of SPOCK1 in PC-9-GR cells. Bioinformatics analysis indicated that SPOCK1 is one of the target genes of miR-1243, and miR-1243 may function as

a tumor oncogene in regulating apoptosis of T790M mutant gefitinib resistant cells. Knockdown of SPOCK1 significantly increased radiosensitivity in PC-9 cells. Early radiotherapy for patients with advanced NSCLC could eradicate T790M subclones, providing evidence for the benefits of early local treatment in TKI-resistant NSCLC patients. [31]

For patients with solitary brain metastases, including large lesions, postoperative SRS can achieve local control as well as WBRT combined with surgery and can spare 58.4–81% of patients from undergoing WBRT.

NSCLC brain metastasis patients can benefit from RT combined with immunotherapy, but their efficacy and safety of combination therapy have not been elaborated thoroughly. The mechanisms of action of the combination of RT and immune checkpoint inhibitors (ICIs) are mainly altering immunogenic cell death, increasing BBB permeability, and activating the antitumor response by enhancing immune activity. This indicates a synergistic effect of the combination of RT and immunotherapy, but the relationships between their mechanisms of action and the currently known mechanisms remain to be further explored.[32] At present, most studies are still in the preclinical stage, and more studies are needed to draw firmer conclusions. RT combined with ICIs has a relatively high control rate of intracranial progression and yields a better prognosis.[33]

Systemic Treatment

Chemotherapy

Chemotherapy is an important treatment for NSCLC patients, but conventional chemotherapeutic drugs cross the BBB at too low amounts, resulting in poor efficacy for patients with brain metastases. Brain metastasis can disrupt the BBB, and in both primary and metastatic brain tumors, the integrity of the BBB is altered, becoming more permeable and forming the so-called brain–tumor barrier (BTB), which allows a portion of chemotherapeutic drugs to enter the cerebrospinal fluid to exert their effects.[34] Pemetrexed combined with cisplatin, a first-line treatment for patients with asymptomatic NSCLC brain metastases, has favorable efficacy.[35] After WBRT, maintenance therapy with pemetrexed combined with cisplatin can improve the intracranial control rate in patients with NSCLC brain metastases. Temozolomide can cross the BBB in high amounts and exert antitumor effects, so it is often used in the clinical treatment of patients with recurrent and progressive brain metastases. Temozolomide with sequential or concurrent WBRT can improve the local control rate of patients with brain metastases, providing a new treatment option for NSCLC patients with brain metastases.[36]

SPOCK1 functions to maintain the BBB. The appropriate downregulation of SPOCK1 can temporarily open the BBB to increase the efficacy of chemotherapeutic drugs. When the BBB is disrupted, the chemotherapy response is significant, and radiation can also disrupt the BBB, but disrupting it has not seemed to improve patient prognoses much.[37] In lung adenocarcinoma, *CHD1L* knockdown reduces the invasion and metastasis ability of lung adenocarcinoma cells. Moreover, SPOCK1 and the EMT-related genes vimentin and MMP2 protein level decrease. CHD1L can confer cisplatin resistance by upregulating the CHD1L–ABCB1–NF-κB signaling pathway.[38] SPOCK1 is upregulated in NSCLC cells resistant to third-generation EGFR-TKIs. Whether SPOCK1 acting downstream of the CHD1L–ABCB1–NF-κB signaling pathway is regulated by CHD1L to confer resistance to third-generation EGFR-TKIs remains to be confirmed.

Targeted Therapy

NSCLC driver genes mainly include EGFR, anaplastic lymphoma kinase (ALK) fusion gene, *RET* gene fusion, *ROS1* fusion, and other rare genes. The *EGFR* gene, encoding a tyrosine kinase, is the most often mutated. Early TKIs usually provide robust systemic disease control for patients with oncogene-driven NSCLC, although these drugs usually fail to accumulate to therapeutically relevant concentrations in the CNS due to their inability to cross the BBB.[39]

Among the EGFR-TKIs, the three targeted drugs, gefitinib, erlotinib, and afatinib have limited ability to cross the BBB, while the third-generation drug, osimertinib, has good ability to cross the BBB.[35] Preclinical studies have shown that osimertinib has better CNS drug penetration than erlotinib or gefitinib and results in sustained tumor regression. The poor prognosis of NSCLC comes largely from its high drug resistance rate. Some scholars have proposed a large-dose "pulsatile" regimen, as this can delay neurological progression and the appearance of new intracranial lesions in patients with brain metastases. The main upregulated genes in drug-resistant tumor cells include SPOCK1, ANKRD1, MYL9, and TENM2. In particular, the downregulation of SPOCK1 inhibits the growth of osimertinib-resistant cell lines and overcomes drug resistance, indicating that SPOCK1 plays a positive regulatory role in osimertinib resistance and may

become a new therapeutic target.[40] Compared with osimertinib monotherapy, osimertinib plus platinum-pemetrexed showed improved efficacy against CNS metastases, including a delay in CNS progression.[41] Furmonertinib is also a third-generation EGFR-TKI. The FURLONG study found that among patients with measurable or nonmeasurable CNS lesions, the CNS progression-free survival time was 20.8 months for patients who received furmonertinib and 9.8 months for patients who received gefitinib. In patients with *EGFR*-mutated NSCLC with CNS metastasis, first-line treatment with furmonertinib showed better efficacy than that with gefitinib in terms of CNS progression-free survival, CNS objective response rate, and CNS depth of response.[42]

The first-generation ALK-TKI crizotinib has a limited ability to cross the BBB; most patients develop drug resistance within a year after starting crizotinib treatment.[43] The second-generation alectinib and the third-generation lorlatinib have better CNS penetration than crizotinib and have better efficacy against ALK-positive NSCLC brain metastases.[44] Second-generation ALK inhibitors such as ceritinib, alectinib, and brigatinib have achieved good treatment results in patients with brain metastases. Alectinib can reach high concentrations in the cerebrospinal fluid, but the problem of ALK inhibitor resistance has not yet been resolved. In terms of the intracranial objective response rate, alectinib is superior to crizotinib, and the risk of CNS progression associated with alectinib is lower.[45] The third-generation drug lorlatinib has a stronger ability to penetrate the brain, but its significant shortcoming is the occurrence of neurocognitive adverse events. These events are rarely severe, but they can cause physical and mental disabilities. According to an observational prospective study carried out in three Dutch university hospitals, among various neurocognitive tests conducted, only the Hopkins Verbal Learning Test-Revised parts b and c showed a significant and clinically relevant decrease at 2 weeks after lorlatinib use. However, these scores returned to baseline at the 2-month assessment. The questionnaire did not produce significantly different results over time. Lorlatinib treatment did not lead to sustained or significant decreases in any specific neurocognitive domain, confirming its safety.[46]

There are also some rare gene mutations such as ROS1 positivity, BRAF mutation, MET gene rearrangement, and HER2 positivity. New drugs have emerged steadily with ongoing research. Taletrectinib is used to treat ROS1-positive patients. A drug evaluation of Phase I and Phase II data suggested that taletrectinib has the potential to improve progression-free survival because of its stronger efficacy for and high CNS penetration into ROS1+ tumors. Compared with other ROS1+ inhibitors, taletrectinib has a better safety profile because of its ability to selectively inhibit wild-type ROS1 and its non-inhibition of TRKB.[47] Entrectinib is a specific TKI targeting the fusion of the NTRK and ROS1 genes, and it can inhibit the kinase activities of TRKA, TRKB, TRKC, and ROS1. A comprehensive analysis of three Phase 1–2 trials by Drilon et al revealed that entrectinib has durable disease control activity in *ROS1* fusion–positive NSCLC patients, is well tolerated, and has a manageable safety profile, making it suitable for long-term dosing in these patients.[48]

Immunotherapy

The immune checkpoint genes identified so far include CTLA4, PD1/PDL1, LAG3, B7H3, B7H4, VISTA, CEACAM1, and BLTA. The most used ICIs for lung cancer treatment are a CTLA-4 monoclonal antibody (mAb) and a programmed death 1 (PD-1)/programmed death ligand 1 (PD-L1) mAb. Now ICIs have undergone extensive clinical research (Table 1).

Brain metastatic cells usually exhibit immune cell infiltration before treatment with ICIs. Despite their uncertain penetration, ICIs can penetrate the BBB and the blood-tumor barrier. In theory, ICIs can directly penetrate the CNS, causing the activation of local immune cells and the expansion of effector cells to reduce the growth of tumor cells.[64] Moreover, the immune microenvironment of the brain is in an immunosuppressive state, there are tumor-infiltrating lymphocytes around brain metastatic lesions, and the expression level of PD-L1 in brain metastatic lesions is high. Phillips et al evaluated the efficacy and treatment-related adverse effects of PD-1/PD-L1 immunotherapy for brain-metastatic NSCLC, concluding that compared with chemotherapy alone, the use of PD-1/PD-L1 inhibitors alone or combination chemotherapy improves overall survival and progression-free survival and leads to a better prognosis.[65]

We have three approved PD-1/PD-L1 inhibitors for patients with PD-1 expression >50% (pembrolizumab, atezolizumab, cemiplimab, and nivolumab). Among them, atezolizumab provides much benefit for overall survival, significantly greater than that of docetaxel in patients with CNS involvement.[66] Patients with NSCLC without driver mutations and with asymptomatic or mildly symptomatic brain metastases should be treated with first-line immune checkpoint

Table 1 Immunotherapy in NSCLC BM

Study	Num. of all Patients	Num. of Patients with BM	BM Population Included	Treatment Group	Control Group	ORR (Num. %)	DOR (Num. %)	mPFS for Patients with BM	mOS for Patients with BM	Other
Sarah B Goldberg et al[49]	42	37 (PD-L1≥1%)	NSCLC with treated and untreated BM	Pembrolizumab	None	29.7%	6.9 months (IQR 3·7 to 22·4 months)	1·9 months (95% CI 1·8-3·7 months	9·9 months (95% CI, 7·5-29·8 months	Four of 42 patients (9·5%) discontinued treatment due to drug-related toxicity Incidences of treatment-related adverse events:14.3%
Sarah B Goldberg et al[50]	36	18	NSCLC with treated and untreated BM	Pembrolizumab	None	33%	NR	NR	7.7 months (95% CI, 3.5 to NR)	None
Shirish M Gadgeel et al[51]	123	At 61 Do 62	NSCLC with treated and untreated BM	Atezolizumab (At)	Docetaxel (Do)	13.7% VS 11.8%	NR	NR	16 months VS 11.9 months	Fewer treatment-related serious adverse events (SAEs) were reported with atezolizumab than with docetaxel
Clément Gauvain et al[52]	43	43	NSCLC with treated and untreated BM	Nivolumab	None	IORR:9% (95% CI: 3–23%)	NR	2.8 months (95% CI:1.8–4.6)	7.5 month(95% CI: 5.6-not reached)	Median intracranial PFS: 3.9 months (95% CI:2.8–11.1)

(*Continued*)

https://doi.org/10.2147/OTT.S483576

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Table 1 (Continued).

Study	Num. of all Patients	Num. of Patients with BM	BM Population Included	Treatment Group	Control Group	ORR (Num. %)	DOR (Num. %)	mPFS for Patients with BM	mOS for Patients with BM	Other
ESCKEYP GFPC study[53]	845	176	74 of them had radiotherapy just before or concurrently with immunotherapy	Pembrolizumab	None	47% (95% CI:39–55%)	NR	9.2 months (95% CI 5.6–15)	29.5 months (95% CI,17.2–not reached)	None
Crino L, et.al[54]	1588	409	Non-squamous NSCLC with asymptomatic BM	Nivolumab	None	19%	NR	3	8.6 months (95% CI: 6.4–10.8)	23 (7%) of whom due to adverse events discontinued treatment.
CheckMate 227[55]	135	135	NSCLC with treated asymptomatic BM	Nivolumab and Ipilimumab (N+I, n1=69)	Chemotherapy (ChT, n2=66)	N+I:33% ChT: 26%	N+I:24.9%, (95% CI,11.3-NR) ChT: 8.4% (95% CI,4.2–13.9)	N+I:5.4 months (95% CI,3.1–8.6) ChT: 5.8 months (95% CI,4.3–8.0)	N+I:18.8 months (95% CI,9.2–29.4) ChT: 13.7 months (95% CI,10.5–16.2)	None
Nadal E et al[56]	40	40	Untreated Brain Metastases	Atezolizumab plus carboplatin and Pemetrexed	None	42.7% (95% CrI, 28.1 to 57.9)	NR	8.9 months	11.8 months (95% CI, 7.6 to 16.9)	2-year OS rate was 27.5% (95% CI, 16.6 to 45.5).
NCT04211090[57]	45	45	Untreated Brain Metastases	Camrelizumab plus cemetrexed and Carboplatin	None	IORR:52.5% (95% CI: 36.1–68.5)	NR	7.4 months (95% CI: 4.4-NR)	21.0 months (95% CI: 15.9-NR)	None

NIke, LOGiK 2004[58]	30	30	Untreated Brain Metastases	Nivolumab plus ipilimumab combined with Platinum-based chemotherapy	None	IORR:50.0% (95% CI, 33.2–66.8%)	Not reached.	8.1 months	Not reached.	None
Tom L Enright et al[59]	77	77	NSCLC with BM	SRT+ICI (n1=33)	SRT (n2=44)	NR	NR	NR	13.9 months	None
Guixiang Liao et al[60]	70	70	NSCLC with BM	WBRT+anti-PD-1 (WA, n1=29)	First line platinum-based chemotherapy or anti-EGFR therapy along with WBRT (W, n2=41)	NR	NR	WA:12 months W:7 months (p=0.247)	WA: not reached W:15 months (95% CI, 11.5–18.4)	There was no significant difference between the treatment cohorts in terms of adverse events
Muhammad Khan et al[61]	21	21	NSCLC with BM	WBRT+anti-PD-1 (WA, n1=10)	WBRT +docetaxel	NR	NR	WA: 11 months (95% CI 6.3–15.6) W: 3 months (95% CI 0.8–5.1)	WA:24 months (95% CI not reached) W:13 months (95% CI 9.9–16.0)	None
NCT02696993[62]	13	13	NSCLC with BM	SRS + Ipilimumab + nivolumab	None	INTRACRANIAL OR rate was 38%	NR	NR	Not reached	(grade ≥3) AEs: 31%; experienced cerebral edema: 15%
Julie L. Koenig et al[63]	97	97	NSCLC with BM	SRS+ICI	None	NR	NR	NR	48.6% vs 25.4% at 1 year; multivariable HR, 0.57; 95% CI, 0.33e0.99; P [0.044)	None

Abbreviations: BM, Brain metastasis; ORR, objective response ratio; DOR, Duration of response; mPFS, median progression-free survival; OS, median overall survival; ORR, intracranial objective response ratio; RT, radiotherapy; WBRT, whole brain radiotherapy; SRS, stereotactic radiosurgery; AEs, Adverse Events; SAEs, Serious Adverse Events; NR, not reported; ICI, Immune checkpoint inhibitors.

https://doi.org/10.2147/OTT.S483576

inhibitors (PD-L1 expression ≥ 50%) alone, or chemotherapy combined with ICIs (PD-L1 expression < 50%), either with pembrolizumab or nivolumab. Dual immunotherapy with programmed death 1 (PD-1) inhibitor and cytotoxic T-lymphocyte associated protein 4 (CTLA-4) inhibitor, with or without combination chemotherapy, shows significant control of brain metastases.[67]

Hu's team discovered that SPOCK1 is associated with the formation of an immunosuppressive tumor microenvironment in lung adenocarcinoma. In terms of immune infiltration, SPOCK1 is positively correlated with the infiltration of cancer-associated fibroblasts, myeloid-derived suppressor cells, tumor-associated macrophages, and regulatory T cells; and SPOCK1 is involved in angiogenesis, fibroblasts, pro-tumorigenic immune infiltration, and the EMT proliferation tumor microenvironment score. In addition, there is a strong correlation between SPOCK1 expression and TGF-β response score. The expression of SPOCK1 and of PD-L1 are positively correlated at both the mRNA and protein levels, indicating that SPOCK1 may play a regulatory role in modulating the immunosuppressive microenvironment through PD-L1. Hu's team reported that SPOCK1 expression is negatively correlated with $CD8^+$ T-cell infiltration in lung adenocarcinoma.[20]

Radioresistance is one of the leading causes of RT failure. Conventional fractionation RT may upregulate PD-L1 expression. PD-L1 induces radioresistance by stimulating cell migration and promoting epithelial–mesenchymal transition (EMT), and radioresistance can be reversed by blocking PD-L1 expression.[68] RT can increase the permeability of the BBB and can also increase the response of NSCLC patients to PD-1/L1 inhibitors, and the combination of the two treatments has a better therapeutic effect without significantly increasing the incidence of adverse events such as radiation-induced brain necrosis.[54,69] Currently, the treatment sequence tends to favor short-interval RT followed by ICI to maximize patient benefit. However, relevant experimental data are scarce, and the optimal timing for sequential treatment is still under exploration.

The Upstream Regulatory Genes of Spock1 Discovered

In the study by Miao et al, it was observed that SPOCK1 expression increased in response to TGF-β treatment, and its expression showed a positive correlation with TGF-β in lung cancer, suggesting that SPOCK1 acts as a positive downstream regulator of TGF-β.[70] The role of TGFβ signaling is also significant in triple-negative breast cancer, where Spock1 expression is upregulated upon TGFβ stimulation.[71] Fan et al identified SPOCK1 as a novel TGF-β-induced myoepithelial marker and further demonstrated its association with enhanced invasion and poor prognosis in breast cancer clinical samples.[15] In the liver, CHD1L regulates Spock1. CHD1L activates the expression of SPOCK1, which then activates Akt signaling to inhibit apoptosis and invasion of HCC cells both in culture and mice.[72] Furthermore, Spock1 has been identified as a target gene of miR155-5p in prostate cancer; miR-155-5p may act as a tumor suppressor gene by inhibiting SPOCK1-mediated progression of prostate cancer.[73] In ovarian cancer, high levels of CHD1L protein were detected in untreated samples but disappeared after chemotherapy. It remains unclear whether the relationship between SPOCK1 and CHDIL in ovarian cancer mirrors that seen in liver cancer; therefore, more studies are needed to clarify this issue.[74]

Summary and Prospects

As our understanding of the treatment methods for NSCLC brain metastases grows, patients with brain metastases have seen significant benefits. SPOCK1 is upregulated in lung adenocarcinoma tissues, and its higher expression is associated with poor prognosis. SPOCK1 signaling contributes to the formation of the BBB and the maintenance of its protective characteristics. Its high expression activates a variety of malignant oncogenic signaling pathways, influencing various NSCLC treatment methods.

Upregulation of SPOCK1 promotes tumor metastasis from the lung to the brain. SPOCK1 also inhibits tumor cell apoptosis, promotes tumor invasion and metastasis, and can be used as a marker for predicting osimertinib resistance and a therapeutic target. Its high expression is correlated with poor prognosis of NSCLC. Therefore, it may become a therapeutic target. Downregulation of SPOCK1 can temporarily open the BBB to facilitate the entry of chemotherapeutic drugs, targeted drugs, and immune drugs to bolster their efficacy.

In summary, the current evidence indicates that SPOCK1 may become a therapeutic target for lung cancer metastases to the brain. In the future, we should make efforts to conduct clinical trials on SPOCK1 inhibitors to test their ability to treat NSCLC patients with brain metastases. Research on the treatment of NSCLC brain metastases is ongoing, and some specific drugs, such as those that increase the permeability of the BBB, are under development. We hope that this review article can provide a basis for drug research, and we look forward to better survival outcomes for patients with brain metastases.

Funding

The funding for the design, collection, analysis and writing of the manuscript was provided by CHEN XIAO-PING FOUNDATION FOR THE DEVELOPMENT OF SCIENCE AND TECHNOLOGY OF HUBEIPROVINCE (CXPJJH124001-2488), Liaoning Provincial Department of Education Research Fund Project (LJKZ0861) and Dalian Municipal Science and Technology Bureau(0122023103).

Disclosure

The authors report no conflicts of interest in this work.

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