Research progress on meningeal metastasis of lung cancer

Abstract

Meningeal metastases (LM) are a common complication of malignant tumors that progress rapidly and have a poor prognosis. Meningeal metastasis may be a combination of intracellular and extracellular factors. The linkage between the C3 signaling pathway and the EGFR ligand regulatory protein pathway may be one of the reasons why NSCLC patients with EGFR mutations are prone to brain/meningeal metastasis. Cerebrospinal fluid cytology is the gold standard for diagnosing meningeal metastases. There are various clinical treatment options, including chemotherapy, radiation therapy, immunotherapy, targeted therapy, and so on. The incidence rate of meningeal metastatic carcinoma is increasing year by year. This article reviews the research progress in pathogenesis, diagnosis and treatment of meningeal metastatic carcinoma of lung cancer.

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Introduction and Epidemiology

Meningeal metastasis (LM), also known as meningeal cancer or cancerous meningitis, is a diffuse, multifocal, and localized infiltration of malignant tumor cells in the meninges, subarachnoid space, and cerebrospinal fluid chambers. It can occur in all malignant tumors and cause serious consequences.Although any systematic cancer has the risk of meningeal metastasis, most of the meningeal metastasis of solid malignant tumors comes from primary breast cancer and lung cancer. The incidence of LM in non small cell lung cancer (NSCLC) is about 3%~5%, of which 84% -96% are adenocarcinoma, about 1/3 LM is combined with brain parenchyma metastasis [2], about 5-8% of solid tumors and 5% -15% of blood malignancies have leptomeningeal metastasis, Studies have shown that its incidence is constantly increasing [1-5].The diagnosis of meningeal metastasis requires the discovery of malignant tumor cells in cerebrospinal fluid (CSF) or changes in meningeal signal on MRI with clear symptoms.The driver gene positive NSCLC is more prone to LM than the wild-type [6]. Due to the presence of the blood-brain barrier, the prognosis of LM patients is poor. If left untreated, the survival time is only 6-8 weeks [7]. With the breakthrough progress of targeted drug therapy and immunotherapy, the overall survival of NSCLC patients with targeted gene mutations has improved, and the incidence of meningeal metastasis in corresponding EGFR and other mutation subgroups has increased. Non small cell lung cancer (NSCLC) patients, especially those with epidermal growth factor receptor (EGFR) mutations,The likelihood of developing LM is more than three times that of EGFR wild-type tumor patients.A retrospective study by Li et al. revealed that the incidence of leptomeningeal metastasis was 3.4% among

5387 lung cancer patients, with EGFR mutations occurring more than 5 times more frequently than EGFR negative patients (9.4% vs. 1.7%) [8-11].

Pathophysiology

The pathophysiology of meningeal metastasis involves a multifactorial process in which tumor cells spread from the primary site. Crossing the vascular system and entering the cerebrospinal fluid site for seeding, due to the abundant vascular system, fibroblasts, infiltrating immune cells, and extracellular matrix ecosystem in the pia mater [12-13], the progression of metastatic diseases in this area may be a combination of intracellular (such as gene expression, metabolism, glycosylation) and extracellular (such as brain microenvironment) factors. The pia mater wraps around the brain and spinal cord, and contains cerebrospinal fluid. Due to the presence of numerous anastomotic branches between cerebral blood vessels and the vertebral artery and venous plexus supplying the brain, as well as anastomotic branches between pulmonary blood vessels and vertebral veins, lung cancer cells can directly pass through the heart and carotid arteries to the brain without being filtered by pulmonary capillaries, leading to blood metastasis [14].At present, the main pathways for tumor cell metastasis to the meninges include direct invasion of adjacent lesions such as brain parenchyma, dura mater, and skull; Lymphatic diffusion around nerves and blood vessels; The specific mechanism of hematogenous dissemination is not yet fully understood, but studies have shown that tumor cells play an important role in reshaping the microenvironment, with matrix derived factor-1 α The two factors, vascular endothelial growth factor and vascular endothelial growth factor, respectively promote the entry of tumor cells into the central nervous system and increase the blood supply to metastatic tumors [15-17]. In addition, tumor cells that metastasize to the meninges will exhibit extensive genomic differences from primary tumor cells, leading to different responses to treatment. Once LM occurs, tumor growth can lead to neurological dysfunction, inflammation, and hydrocephalus in the brain. The obstruction of the blood-brain barrier (BBB) by drugs can create conditions for the proliferation of tumor cells, resulting in death events and adverse consequences for LMC patients [18-19].

Pathogenesis

Due to the presence of the blood-brain barrier, it is important for tumor cells with meningeal metastasis to obtain the growth factors and nutrients needed for growth in unsuitable cerebrospinal fluid. CSF (with full English name and abbreviation) is mainly composed of Na+, HCO3-, and a small amount of K+, Mg++, Ca++, with low protein, glucose, and cytokine content.A study has found that cancer cells host interactions, in which malignant cells overcome the epithelial barrier and actively enrich cerebrospinal fluid with plasma derived components [20]. The most crucial one is the Complement protein C3.Pial meningeal metastatic cancer cells grow in cerebrospinal fluid by secreting C3. C3 disrupts the blood CSF barrier through its receptor C3aR on the choroid plexus, allowing for the selection of plasma components, including growth factors such as double regulatory proteins, and other substances, to enter CSF and promote cancer cell growth [21-23].The C3 signal transduction pathway may allow EGFR ligand regulatory proteins to enter CSF [24]. 9% to 10% of NSCLC patients with EGFR mutations will progress to LM at initial diagnosis or during treatment with

tyrosine kinase inhibitors (TKIs) [25-26]. A multicenter real-world study of tumor DNA from cerebrospinal fluid in the NSCLC genome map of CNS metastasis showed that the detection rate of EGFR mutations in cerebrospinal fluid was significantly higher than in plasma [27]. The linkage between the C3 signaling pathway and the EGFR ligand regulatory protein pathway may be one of the reasons why NSCLC patients with EGFR mutations are prone to brain/meningeal metastasis.

Clinical diagnosis

The diagnosis of LM is mainly based on a comprehensive evaluation of neurological symptoms, imaging evidence, and cerebrospinal fluid data. Cerebrospinal fluid cytology examination remains the gold standard for LM diagnosis: sensitivity is 75% -90%, specificity is 100%; The detection rate for repeated three tests is greater than 90% [28]. However, due to the relative difficulty in accessing LMC tissues, the lack of cells in CSF during the sampling process, and the rapid death of patients, the development of diagnostic techniques for LMC patients is facing numerous challenges [29-30].The recent research results combining liquid biopsy methods with next-generation sequencing techniques have made it possible to analyze circulating tumor cells, circulating tumor DNA (ctDNA), and cell free RNA derived from CSF [31].Other diagnostic techniques include meningeal biopsy, CSF liquid biopsy, CSF circulating tumor cells (CTC), and CSF biomarkers. CtDNA refers to extracellular DNA released by cancer cells through various mechanisms, such as active secretion and/or passive release during cancer cell death.In 2015, Pan and colleagues reported the first use of next-generation sequencing technology to analyze ctDNA derived from CSF in LMC.In 2015, De Mattos Arruda and his colleagues confirmed that CSF derived ctDNA captured the mutation landscape of various central nervous system tumors, including LMC, with higher sensitivity compared to plasma derived ctDNA [33-34].Cerebrospinal fluid analysis has great potential for the diagnosis of LMC, the genetic and epigenetic characteristics of the disease, and the determination of treatment resistance mechanisms.Multiple ctDNA analyses targeting non-small cell lung cancer are used to detect driving genes in cerebrospinal fluid and assist in the treatment of patients [35-37].The 2021 WCLC conference reported that Professor Wu Yilong's team used ctDNA testing in cerebrospinal fluid to guide targeted treatment for patients with meningeal metastases and achieved good results.Therefore, dynamic monitoring of cerebrospinal fluid ctDNA to identify the unique gene profile of brain metastases can better predict intracranial tumor remission in NSCLC patients with brain metastases [38].

Clinical treatment

NCCN has released comprehensive guidelines to stratify patients with central nervous system cancer and determine which patients should receive active treatment [39]. The treatment principle for LMC patients is to improve neurological function, prolong survival, and prevent further neurological deterioration. Therefore, multidisciplinary consultation is crucial for individual treatment [40]. LMC has traditionally been treated with whole brain radiotherapy (WBRT), central nervous system penetrating systemic therapy, and palliative therapy. Due to the limited ability of most systemic chemotherapy drugs to pass through the blood-brain barrier, they are usually combined with radiotherapy to slow down neurological decline, stabilize quality of life, and slightly prolong survival.The current main treatment methods

include molecular targeted therapy, systemic chemotherapy, intrathecal infusion chemotherapy, local radiotherapy, immunotherapy, etc. [41]. There is currently no standard treatment plan for leptomeningeal metastasis. In clinical studies, patients with leptomeningeal metastasis mainly receive whole brain radiotherapy (WRBT), chemotherapy, and targeted therapy (TKI).According to multiple research findings, the treatment of EGFR mutated leptomeningeal metastasis should be prioritized with low efficacy and high toxicity targeted drugs, especially TKI therapy for patients with poor physical fitness.Suitable treatment plans should be tailored according to individual patient conditions [42-44].

Radiotherapy

Retrospective studies have shown that radiotherapy cannot prolong the overall survival (OS) of LMC patients, but it can significantly alleviate symptoms and may improve drug penetration by interfering with the blood-brain barrier (BBB), thereby improving the quality of life of symptomatic disease patients [45-48].The scope of radiotherapy is determined by the degree of influence on the neural axis, with local radiotherapy being given priority. Whole brain radiation therapy (WBRT) is more commonly used for the treatment of meningeal metastases, especially in cases with brain metastases (BMs), combined with systemic drug therapy and other treatments. Focused skull base radiation therapy can treat different types of cranial nerve lesions. In order to avoid the risk of harmful neurocognitive effects associated with WBRT, stereotactic radiotherapy (SRS) has increasingly been used as an alternative to WBRT [59-50].Patients who have improved their symptoms through radiation therapy only appear when the radiation dose is low and the symptom duration is short, while those with longer symptom duration have almost no benefits [51-52].

Chemotherapy/intrathecal chemotherapy

In theory, tumor cell brain metastasis can partially disrupt the blood-brain barrier, which is beneficial for the penetration of chemotherapy drugs. However, in clinical practice, the effect of conventional chemotherapy drugs is not ideal [53]. Studies have shown that the entry of drugs into cerebrospinal fluid is the result of a combined effect of the mechanisms of inflow and outflow from the blood-brain barrier. The inflow mechanism includes absorption endocytosis, receptor mediated transport, carrier mediated transport, intercellular hydrophilicity pathway, and intercellular lipophilicity pathway, while the outflow mechanism is mediated by P-gp, BRCP, etc. [54-55].Pemetrexed is an anti folate synthetic anti-tumor drug.A retrospective analysis suggested that the median OS for patients who used pemetrexed after LM was 13.7 months vs. 4.0 months for those who did not use it (P=0.008). Multivariate analysis showed that the use of pemetrexed after LM was associated with better survival (HR=3.1, 95% CI: 1.5-6.3; P=0.002) [56].

Intrathecal injection (IT) chemotherapy is the direct delivery of cytotoxic drugs to the site of ventricular disease and tumor cells present throughout the cerebrospinal fluid.Bypassing the blood-brain barrier can also reduce the dosage of chemotherapy, reduce the likelihood of systemic toxic side effects, and allow sufficient drug concentration to be administered throughout the cerebrospinal fluid in the case of diffuse metastasis [57-58]. The two main routes of intrathecal chemotherapy include lumbar puncture (LP) or through ventricular reservoir (translation requires verification and calibration) (such as Ommaya sac).The

advantages associated with the use of Ommaya capsules include better distribution in the cerebrospinal fluid chamber, avoidance of repeated LPs, and easier administration.The half-life of intrathecal administration is short, and the drug concentration drops to sub therapeutic levels within a few hours and is completely eliminated within 1-2 days.Methotrexate (MTX), Ara C, and thio TEPA are three commonly used drugs for intrathecal treatment of LM patients [59]. Other commonly used drugs include Topotecan and Ara C sustained-release liposomes, so the number of available drugs is limited compared to those that can be administered systemic. In addition, some new drugs such as targeted drugs and temozolomide are also actively trying intrathecal injection.For LM patients with high tumor cell load in CSF, intramuscular administration of Ommaya is superior to lumbar puncture administration. However, in a study targeting meningeal metastasis, compared to methotrexate, intrathecal injection of methotrexate did not show an increase in survival rate [60].Add recently published literature on partial intrathecal infusion (IT) chemotherapy, such as pemetrexed (effective rate, PFS, etc.)

Immunotherapy

At present, immune checkpoint inhibitors (ICIs) are the first-line standard treatment for locally advanced/metastatic NSCLC [61]. Due to the fact that most clinical trials have largely excluded patients with LM, there is limited data on ICIs for treating LM. LMC patients have a relatively weak response to immunotherapy, partly due to limited delivery of systemic drugs to the central nervous system. The molecular weights of pembrolizumab, nivolumab, and ipilimumab are all ⩾ 145 kDa (thousand daltons), which makes penetrating the blood-brain barrier and blood-brain spinal fluid barrier challenging [62].Anti PD1, anti PD-L1, and anti CTLA-4 drugs have all been shown to be effective against NSCLC and melanoma brain metastasis, but there is no data indicating significant benefits for NSCLC patients [63-64].Hendriks et al. retrospectively analyzed 19 patients with NSCLC meningeal metastasis treated with ICIs. Some non-small cell lung cancer patients with LM did benefit from ICI treatment, especially those with good prognosis in NCCN LM who achieved longer survival [65]. A phase II study evaluated the combined use of nivolumab and ipilimumab in 18 patients with LMC, reporting an OS of 44% at 3 months [66].Immunosuppressants have potential mechanisms for treating brain metastases through both local and systemic effects, and further research is needed on the efficacy of ICIs in treating LM. Multiple phase II trials are currently underway, and results describing the efficacy of PD-1 inhibitors pembrolizumab and nivolumab are highly anticipated (NCT02886525, NCT04729348).Meanwhile, research involving PD-L1 inhibitors Durvalumab and Avelumab has begun [67]. With the development of various clinical studies in the field of non-small cell lung cancer, the overall trend of immunotherapy is gradually moving from the back line to the front line, and from single drug to more and more combination models.

Targeted therapy

LM can be classified into EGFR sensitive mutation NSCLC meningeal metastasis, ALK gene fusion NSCLC meningeal metastasis, ROS-1 fusion NSCLC meningeal metastasis, etc. based on its sensitive driving genes [68-69].China is a major country in lung cancer, and the EGFR mutation rate in Asian populations is higher than that in European and American populations.

Therefore, the focus of targeted drugs in China is on EGFR sensitive mutations. With the widespread application of TKIs, the survival period of LM in NSCLC patients with driver gene positivity is significantly prolonged.EGFR TKIs are small molecule like agents, however, their penetration rate into cerebrospinal fluid is still relatively low. Therefore, the intracranial treatment effect of the first generation EGFR TKIs is not ideal, mainly due to pharmacokinetic failure. Recent studies have reported that the relief effect of the second generation Dakotinib on the intracranial is similar to that of the third generation [68, 70].However, third-generation TKIs have shown different therapeutic effects. Oxetinib is the third-generation oral EGFR-TKI, which effectively and selectively inhibits EGFR-TKI sensitization and EGFR T790M resistance mutations.Pre clinical and Phase I/II clinical studies have shown that ositinib has higher brain permeability than first and second generation treatments, and ositinib achieved a first-line PFS of 18.9 months in the FLAURA study.Oxetinib is superior to the first and second generation in treating NSCLC with EGFR mutations for meningeal metastasis.Saboundji et al. retrospectively analyzed 20 NSCLC-LM patients treated with ositinib, of which 13 had EGFR-T790M resistance mutations. The total median OS and PFS of the 20 LM patients were 18.0 months and 17.2 months, respectively. Therefore, regardless of the presence of T790M resistance mutations, ositinib had significant therapeutic effects on LM patients [71-72].In 2022, ASCO reported CNS data for two third-generation EGFR TKIs: a study of amitinib and a study of fumetinib.The research results show that the clinical efficacy of third-generation EGFR TKIs in treating CNS metastasis is superior to that of the first generation. In addition, a retrospective study of multiple combinations of amitinib and anti angiogenic drug bevacizumab in the treatment of EGFR mutated meningeal metastasis NSCLC has confirmed that amitinib or bevacizumab/ami combination chemotherapy regimens have significant therapeutic effects on EGFR mutated positive meningeal metastasis patients.The median treatment time for the combination of amitinib and bevacizumab was 11 months, with a median PS score of 4 before treatment and 1 after combination therapy [73].Other new TKIs with high brain penetration rates are being developed, which are expected to improve the efficacy of patients with brain and meningeal metastases. Further clinical research data is expected. For the LM of NSCLC caused by mutations in the ALK gene, the new generation ALK inhibitor alectinib showed significant CSF penetration and activity in NM [74].ASCEND-7 studies have shown that Seretinib treatment for ALK+NSCLC brain and/or meningeal metastases can produce clinically significant high and sustained intracranial and extracranial remission [75].Another study suggests that loratinib can successfully treat ALK positive NSCLC patients with meningeal metastasis, and the small molecule macrocyclic amide structure of loratinib may be its advantage in crossing the blood-brain barrier (BBB) [76-77].

Summary

LM is a catastrophic result of the spread of systemic cancer.The current treatment options are mainly palliative treatment, which cannot significantly prolong the survival of patients. The mechanism of meningeal metastasis is not yet clear, but tumor cells may play an important role in reshaping the microenvironment. Cerebrospinal fluid genetic testing plays a preliminary role in identifying driving genes and predicting intracranial remission. In the future, the third-generation TKI combined chemotherapy regimen has shown initial efficacy for patients with meningeal metastasis. Currently, multiple studies are being conducted,

especially the combination of TKIs with other treatment methods. We look forward to more relevant data being released.

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