Topical Issue on Cancer Signaling, Metastasis and Target Therapy **Open Access**

Review article

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The proceedings of brain metastases from lung cancer

DOI 10.1515/biol-2016-0016

Received April 29, 2016; accepted June 7, 2016

Abstract: Brain tumors include primary tumors of various intracranial tissue and secondary intracranial tumors that transferred from other parts of the body. Secondary intracranial tumors are especially prevalent in patients with lung cancer. The mechanisms of lung cancer with brain metastases are complicated, they are affected by a variety of factors. Thus, identifying the mechanisms of lung cancer with brain metastases will have far-reaching meanings both for clinic pharmacy research and for a better quality of life for patients; Brain metastases from lung cancer represent a prevalent and challenging clinical dilemma, and some research suggests that the outcomes and characteristics of brain metastases that result from lung cancer primary sites are perhaps different than those from other primary sites, therefore increasing the difficulty of clinical treatment. Despite steady research developments during recent years, the survival rates remain poor. The mechanisms and therapeutic options for treating brain metastases arising from lung cancer are review in this article.

Keywords: lung cancer; brain metastases; molecular targeting treatment; chemotherapeutics;

1 Introduction

Approximately 150,000-170,000 patients with cancer develop into brain metastasis each year in the United States, making this the most common complication of systemic cancer. Lung cancer's primary tumors are the most frequent source of brain metastases, accounting for approximately 48%-60% of all those diagnosed [1]. Brain metastases of patients with lung cancer include both non-small-cell (NSCLC) and small-cell (SCLC) histologists [2]. Brain metastases (BM) from non-small cell lung cancer (NSCLC) are about 20%, autopsy up to 40% [3]. Approximately 10% of SCLC patients have brain metastases (BM) at diagnosis and an additional 40% will develop central nervous system (CNS) involvement during their disease course [4], 2 years later, it can reach 80% [5]. The natural median survival of lung cancer with brain metastasis patients is only about one month [6]. The mechanism of lung cancer with brain metastasis is complicated. Thus, it is a great challenge to prevent and develop therapeutic options for brain metastasis from lung cancer.

2 The mechanisms of lung cancer with brain metastases

Multiple mechanisms are involved in the development and progression of lung cancer with brain metastasis, the main influencing factors of lung cancer with brain metastases are as follows:

2.1 Nerve - immune adjustment factor

Vagal nerves play an important role in the interaction of nervous and immune systems. It can be observed that the incidence and metastases of lung tumors increased after the role of vagal nerves in clinical and animal experiments. An airway sensor is a kind of biological sensor which can identify a variety of mediators and cytokines in the process of lung inflammation, the related signal can be transferred to the brain via vagus and induce the brain metastases, which then generates a series of reactions to regulate the

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growth of tumors and the progression of inflammation. The expression of neurotransmitter receptors in tumor cells make it possible for the direct interaction between neurons and substrates, which provides a pathway for the metastasis of lung cancer cells to the brain [7]. He *et al.* [8] investigated microglial reactions in brain tissues with metastatic lung cancer cells and evaluated the cytotoxic effects of lipopolysaccharide (LPS)-activated microglia on metastatic lung cancer cells in vitro. Their findings suggest that the interaction between neurons and neurotransmitter receptors can motivate lung cancer cells movement to the brain.

2.2 Growing factors and chemotactic factor (CF)

Vascular endothelial growth factor (VEGF) can specifically promote the increase of vascular endothelial cell growth and angiogenesis of permeability. VEGF is conducive to tumor invasion and metastasis and induce tumor vascular formation. It has the strongest effect and specificity of vascular growth factors [9]. Studies have found that high expression of VEGF-C and postoperative recurrence in patients with lung cancer and brain metastases was positively correlated [10]. In the presence of the nearly 70% of patients with NSCLC VEGF-C expression, recurrence within 1 year after operation accounted for 47% of patients, and positive expression of VEGF-C in patients with brain metastasis rate was significantly higher than that of negative expression [10]. EGFR and its expression level is closely related to the degree of tumor invasion and the survival rate of the patients with most epithelial derived tumors, such as lung cancer and brain metastases. In NSCLC patients, the positive rate of EGFR was as high as 43%-89%, which was positively correlated with the distant metastasis and poor prognosis [11]. In NSCLC of brain metastases, 34.8% of patients were found with high expression of EGFR, and about 45% of patients had high expression of HER-2 [12]. Therefore, further study on the mechanism of EGFRs in lung cancer brain metastasis is of great significance to improve the survival rate of patients. Inflammatory chemokines and their receptors are involved in the regulation of tumor cell migration through the interaction between stromal cells and tumor cells, which are involved in the growth and metastasis of tumors [13,14]. The research reported the expression of CXCL12 and CXCR4 can facilitate cancer cells through the blood-brain barrier. At the same time, the expressions of CXCR4 combined with hormone activation can enhance the helper cells (such as mesenchymal cells) emphatically enhance stickiness, which provides favorable conditions for lung cancer with brain metastasis to happen [15].

2.3 Blood-brain barrier (BBB) and K-Ca channels

The blood-brain barrier is a complex system of cells between brain tissue and blood. It is the material basis of brain microvascular invasion, so when cancer cells metastasize, the microvascular system that nourishes the brain tumor is called the blood-brain tumor barrier (BTB). The BTB limits the delivery of therapeutic drugs to brain tumors [16]. The open level of K-Ca channel is positively correlated with the permeability of BTB, and the K-Ca channel is highly opened in lung cancer brain metastasis tumor tissue and brain metastasis, which is significantly higher than that in normal brain tissue [16].

2.4 Carcinoembryonic antigen (CEA) and other related factors

The abnormal expression of some tumor suppressor gene such as CEA, MMPs and other proteins has intimate relationship with lung cancer brain metastasis [17]. D Sun etc. [18] studied the potential mechanisms of miRNA-328 and miRNA-378 for brain metastases in non-small-cell lung cancer. They used real-time polymerase chain reaction to examine the expression of miRNA-328 and miRNA-378 in patients who received a curable surgery for their lung cancer and immunohistochemical staining to examine the expression of N-cadherin, E-cadherin, vascular endothelial growth factor, protein kinase Cα and S100Bm. They found that miRNA-328 might promote brain metastases by regulating the expression of protein kinase Cα.

3 The therapeutic options for treating lung cancer with brain metastases

3.1 Surgical treatment

Brain metastases tumors are usually small, topical, with clear boundarie creating conditions for surgery. With the improvement of diagnosis and surgical techniques, more and more patients accept surgery. Most scholars suggest that brain metastases surgical indications are as follows:

I. The primary tumor site is clear, and it has no other organ metastasis. II. The site of the tumor is superficial, locate in unimportant functional areas. III. The primary tumor has been controlled. IV. The brain metastasis is with acute intracranial hypertension, so the state of illness can be improved by surgery or decompression and survival time can be prolonged. V. The primary tumor site is uncertain, and the property of the tumor needs to be explicit. For large tumors that are located in sub-region with significant intracranial hypertension, surgery is a safe and effective method. For tumors located in important functional areas, surgery is not recommended to prevent postoperative major neurological damage to surrounding tissue. Yoshinaga etc. [19] retrospectively evaluated the effectiveness of surgical treatment for non-small cell lung (stage IV) cancer patients with synchronous brain metastases. They found that adenocarcinoma histology and serum LDH significantly affected survival, and concluded that surgical treatment may be acceptable in a selected group of non-small cell lung cancer patients with synchronous brain metastases. At present, surgery plus whole-brain radiotherapy (WBRT) is advocated to eliminate residual tumors in the brain and other parts of sub-clinical lesions. The median survival period can be extended 16 to 19 months by combining surgery with WBRT [20].

3.2 Radiation therapy

Whole brain radiation therapy (WBRT) is the traditional treatment of lung cancer with brain metastasis. WBRT can improve neurological symptoms, improve the quality of life, improve survival period, and the efficiency is more than 60% [21]. Compared with traditional radiation therapy, stereotactic radiotherapy (SRS) has many advantages, such as little side effects and low risk, so it has been widely used in clinical practice. SRS is a one-time, high-energy X-ray or scattered γ rays converged on the target, forming a very steep dose gradient outside the target area, effectively killing tumor cells, and also maximizing the protection of tumor peripheral tissues [22]. The characteristics of SRS are high precision, safe, fast, effective and reliable, high malignant tumor control rate, non-invasive, low damage and short hospital stay [23]. Yomo *et al.* [24] analyzed 41 consecutive patients with a limited number of BM (≤ 10) from SCLC who received SRS as the initial treatment to investigate whether upfront SRS might be an effective treatment option for patients with BM from SCLC in a retrospective analysis. The results suggested although SRS provided durable local tumor control, repeat treatment was needed in nearly half of the patients to achieve control of distant BM. Brachytherapy seed implantation in lung cancer patients with brain metastases provides a new treatment. A retrospective study of 67 patients showed that surgery plus I^{125} seeds implantation in the treatment of isolated brain metastases of NSCLC can improve the survival rate and improve the quality of life [25]. A retrospective analysis of 40 cases of patients with brain metastases treated by surgery combined with I^{125} brachytherapy, the median survival rate was 11.3 months, 55% of patients went without brain metastasis progression and the method achieves good local control [26].

4 Drug therapy

4.1 Chemotherapeutics

Whole-brain radiotherapy (WBRT) for asymptomatic brain metastases can reduce performance status and delay systemic treatment, so primary chemotherapy can be a feasible alternative treatment [27]. Recent studies [28] showed that the blood-brain Barrier (blood brain barrier, BBB) has been destroyed in the process of brain metastases, and with whole brain radiotherapy, mannitol and other dehydration drugs can make the BBB open in a variety degrees, which allows chemotherapy drugs across the blood - brain barrier into the central nervous system to kill tumor cells. Nitrosourea, cisplatin, teniposide, paclitaxel, vermeer, temozolomide are chemotherapy drugs that have been commonly used [29]. Barlesi *et al.* [30] reported 43 cases of the use of pemetrexed plus cisplatin in chemotherapy treatment of brain metastases from NSCLC, the total effective rate was 34.9%, and median OS was 7.4 months. Ma Chunhua *et al.* [31] reported 27 cases of use for nepal gan, nimustine and carboplatin in chemotherapy treatment for NSCLC brain Transfer by arterial infusion, the total effective rate was 55.56% (15/27), and median OS was 7 months. Many other clinical trials [32-35] have confirmed that platinum-based drugs combined with chemotherapy drugs such as pemetrexed and vinorelbine can benefit NSCLC patients with brain metastases, and it has a high efficiency for intracranial lesions, the median survival is up to 7.4-9.1 months, and the toxicity can be tolerated. Systemic chemotherapy combined with radiation therapy is recommended.

4.2 Molecular targeting treatment

Molecular targeted drugs provide a new tool for the treatment of brain metastases from lung cancer. Epidermal growth factor receptor tyrosine kinase inhibitor gefitinib, imatinib, erlotinib are studied more. Tumour-specific mutations are emerging targets for metastatic brain tumors and could improve overall survival. For example, rearrangement of ALK is seen in about 2–7% of NSCLC, and is a therapeutic target in advanced NSCLC [36]. Crizotinib (Pfizer) is a FDA approved small molecule inhibitor of anaplastic lymphoma kinase gene (ALK), mesenchymal-epithelial transition (MET), and c-ros oncogene 1, receptor tyrosine kinase (ROS1) for use in advanced NSCLC with the ALK rearrangement. Activating mutations or translocations of ALK have been identified in non–small-cell lung cancer [37-41]. A phase 3 trial of crizotinib versus standard chemotherapy in previously-treated advanced ALK-rearranged NSCLC have shown that crizotinib is superior to standard chemotherapy in patients with advanced non-small-cell lung cancer with ALK rearrangement [37]. Alectinib (Roche) was given the FDA designation of a breakthrough therapy. A phase 1/2 investigation of alectinib in crizotinib-naive patients with ALK-rearranged NSCLC showed responses in 93.5% patients (43 of 46 patients) [42]. Besides, Brigatinib (Ariad Pharmaceuticals), another FDA-designated breakthrough therapy, not only inhibits ALK, but also targets EGFR and ROS1. A review of early results from a phase 2 trial of brigatinib showed an even higher intracranial response of 60% in patients with previously untreated or progressing brain metastases [43].

5 Conclusion

Brain metastases from lung cancer represent a prevalent and challenging clinical dilemma associated with poor survival and high morbidity [44]. Van Kaick etc. [45] concluded that of the active and effective treatments, the choice of treatment is the one benefits the patient in the long-term. Although people have done a lot of research about the development and transfer mechanisms of lung cancer brain metastases, the effect of mechanisms of lung cancer with brain metastasis is still not fully understood. Therefore, a better understanding of the mechanisms of brain metastasis is important to improve current therapies and design new treatment modalities [46], that have far-reaching significance in the treatment and prevention of diseases. For now the conclusion is to identify the mechanism of brain metastases from lung cancer, choose postoperative WBRT, SRS, or a combined therapy that complements each other in order to achieve the optimum therapeutic effect, effectively improving the clinical symptoms, quality of life and increasing chances of survival.

Conflict of interest: The authors declare that there is no conflict of interests regarding the publication of this paper.

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