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Perspective

Current progress and outcomes of clinical trials on using epidermal growth factor receptor-tyrosine kinase inhibitor therapy in non-small cell lung cancer patients with brain metastases

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Abstract

Non-small cell lung cancer (NSCLC) continues to be one of the major causes of cancer-related deaths worldwide, and brain metastases are the major cause of death in NSCLC patients. With recent advances in understanding the underlying molecular mechanism of NSCLC development and progression, mutations in epidermal growth factor receptor (*EGFR*) have been recognized as a key predictor of therapeutic sensitivity to EGFR tyrosine kinase inhibitors (TKIs). Using EGFR-TKI alone or in combination with standard treatments such as whole-brain radiotherapy and surgery has been an effective strategy for the management of brain metastasis. Particularly, a newer generation of EGFR-TKIs, including osimertinib and AZD3759, has been developed. These new EGFR-TKIs can cross the blood–brain barrier and potentially treat EGFR-TKI resistance and improve prognosis. In this article, current progress and outcomes of clinical trials on the use of EGFR-TKIs for treating NSCLC patients with brain metastasis will be reviewed.

Keywords: Non-small cell lung cancer; Brain metastases; Epidermal growth factor receptor mutation; Tyrosine kinase inhibitors; Therapeutic outcomes

Introduction

Non-small cell lung cancer (NSCLC) is one of the major causes of cancer-related deaths in the world. As the disease has an insidious onset, many NSCLC patients were diagnosed during stage III–IV with lymph node or distal metastases.[1,2] Brain metastasis refers to cancer cells spreading to the brain parenchyma, meninges, cranial nerves, and intracranial vessels, which leads to acute deterioration of the health status and impairment of the quality of life of the patients. In

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NSCLC patients, approximately 25%–40% of patients will eventually develop brain metastases, which usually occur 2 years after diagnosis of the primary tumor.[3] Even in non-metastatic primary NSCLC patients, approximately 9% will develop brain metastases.[4]

Clinical studies have shown that after the occurrence of brain metastases in NSCLC patients, their survival time will be significantly shortened,[5] and if no corresponding treatment is given, the median survival period is 1–2 months.[6] Epidermal growth factor receptor (*EGFR*) mutations are believed to be factors independent of age, physical status, and extracranial disease; additionally, *EGFR* mutations are an independent risk factor affecting the survival time of NSCLC patients with brain metastases. When compared to patients with wild-type *EGFR*, those with *EGFR* mutations have a significantly longer median survival time.[7] However, another study showed no statistical differences in the incidence of brain metastases between patients with *EGFR* mutations and wild-type *EGFR* , and the brain metastases had no significant effect on the median survival time.[8]

Currently, the treatment methods for NSCLC with brain metastases mainly include surgery, radiotherapy [such as whole-brain radiotherapy (WBRT) and stereotactic radiosurgery (SRS)], and chemotherapy. Surgical resection of brain metastases alone can effectively alleviate tumor compression, but with relatively higher postoperative local intracranial recurrence rate. Qin et al[9] analyzed that the mean median survival time of the patients was 12.7 months in surgery group and 14.85 months in SRS group, respectively. The 1-, 2- and 5-year overall survival (OS) rates of the patients were 59%, 33% and 19% in surgery group, and 62%, 33% and 14% in SRS group, respectively. WBRT or SRS can significantly increase the survival time; however, patients cannot usually tolerate the related complications and adverse reactions. Furthermore, the majority of chemotherapy drugs cannot penetrate the blood–brain barrier (BBB) to enter into tumor tissues, which limits the therapeutic outcomes of systemic chemotherapy in treating NSCLC patients with brain metastases. Epidermal growth factor receptor-tyrosine kinase inhibitors (TKIs) have small molecules used in targeted therapy, and a certain proportion can penetrate the BBB, showing therapeutic effects in patients with NSCLC brain metastases with *EGFR* mutations.[10,11] Considering that NSCLC patients with *EGFR*-sensitive mutations are more prone to brain metastases compared with those with wild-type *EGFR*, TKI treatment for the former should be a good option.[12] This article describes the current treatment progress of TKI treatment for NSCLC patients with brain metastases.

Theoretical foundation of TKI treatment for NSCLC brain metastases

The BBB is composed of endothelial cells, astrocytes, pericytes, and multiple carrier proteins and is one of the internal barriers participating in the innate immunity of the body. The BBB can block pathogens and other macromolecules from entering into the brain tissues and ventricles from the bloodstream.[13,14] It is generally believed that only lipophilic small molecules ($Mr < 400$ Da) can penetrate the normal BBB through diffusion and other transport mechanisms. The majority of chemotherapeutic drugs are hydrophilic macromolecules that cannot penetrate the BBB without the carrier proteins. Furthermore, many multiple drug-resistant efflux pumps exist on the capillary surface of the BBB, such as P-glycoprotein and multidrug-resistant-associated proteins, which can further limit the entry of drugs into the brain tissues.[15]

Drugs used in TKI-targeted therapy have characteristically small molecules, such as gefitinib (446.9 Da) and erlotinib (394 Da). Experiments with the multidrug-resistant PC-6/PTX lung cancer cells showed that gefitinib can directly interact with overexpressed P-glycoprotein and inhibit its drug-efflux function.[16] Therefore, some proportion of TKIs can penetrate the BBB. Clinical studies also found that the BBB penetration rate of erlotinib in NSCLC patients with brain metastases is $(4.4 \pm 3.2)\%$.[17] With increasing doses of TKIs used, their corresponding concentrations in the cerebrospinal fluid (CSF) also increase. Therefore, in patients with brain metastases who do not respond to low concentrations of TKIs, increasing drug concentrations can result in effective disease control.[18–21] In addition, experiments using animal models also showed that when the integrity of the BBB is disrupted, such as when the diameter of the brain metastases is >0.25 mm, its permeability will increase.[22] Wang et al[23] analyzed the CSF of 22 NSCLC patients treated with gefitinib and found that its penetration rate was significantly higher in patients with brain metastases than in patients without brain metastases (1.5% *vs.* 0.9%, $P = 0.010$). This shows that the occurrence of brain metastases may affect the structure of the BBB and increase drug permeability, increasing the concentrations of TKIs in the CSF,