Cancer Letters 351 (2014) 6–12

Contents lists available at ScienceDirect

Cancer Letters

journal homepage: www.elsevier.com/locate/canlet

Mini-review

# Epidermal growth factor receptor tyrosine kinase inhibitors in the treatment of central nerve system metastases from non-small cell lung cancer

Jingze Zhang, Jinming Yu, Xindong Sun, Xue Meng *

*Department of Radiation Oncology, Shandong Cancer Hospital and Institute, Shandong Academy of Medical Sciences, Jinan, Shandong Province 250117, China*

ARTICLE INFO

*Article history:*
Received 23 January 2014
Received in revised form 10 April 2014
Accepted 19 April 2014

*Keywords:*
NSCLC
Brain metastasis
EGFR TKI

ABSTRACT

Brain metastases (BM) are common and disastrous occurrence in patients with non-small cell lung cancer (NSCLC). Currently increasing studies suggest remarkable efficacy and mild toxicity of the epidermal growth factor tyrosine kinase inhibitor (EGFR TKI) in these patients, making targeted therapy an attractive option to BM from NSCLC. We here present a review about the use of EGFR-TKIs in this context and the following questions would be discussed: Are TKIs capable of permeating across brain–blood barrier (BBB)? How to boost exposure of EGFR TKI in cerebrospinal fluid to overcome the resistance of refractory metastases? Would the combination with other treatment like radiotherapy bring about advanced effect? And which patients with BM is the fittest population to EGFR-TKI treatment? In fact, though the administration of EGFR TKI only could achieve certain effect with limited penetration across BBB, increasing dose and combined radiotherapy would carry out better outcome. Unsurprisingly EGFR mutations were still the most important predictor of the sensitivity.



## Introduction

Non-small cell lung cancer (NSCLC), the leading cause of cancer-related mortality for both men and women, has a high risk of brain metastasis that approximately ranges from 20% to 40% [1,2]. The outcomes of brain metastases (BM) from NSCLC are desperate with few effective treatment options. The median overall survival time (OS) of patients without treatment is less than 3 months [3]. The appropriate use of whole-brain radiation therapy (WBRT) supplemented with steroids brings about rapid attenuation of neurologic symptoms and improvement of performance status [4]. For patients with single BM, additional stereotactic radiosurgery may provide advantageous survival [5] and surgery followed by WBRT can achieve better outcomes than WBRT alone [6]. Though local interventions achieve definite effect indeed, yet side effects are inevitable and extracranial disease is left beyond control. Due to poor performance status, patients with BM from NSCLC may not be ideal candidates for surgery or radiosurgery. The requirement to improve the extracranial disease should also be considered. As performance of systemic progress, presence of BM requires systemic treatment. Whereas, because of the impenetrability of brain–blood barrier (BBB) the role of systemic chemotherapy is controversial and has been explored in only a few studies [7,8].

Different from traditional cytotoxic agents, tyrosine kinase inhibitors (TKI) of epidermal growth factor receptor (EGFR), like gefitinib and erlotinib, have been shown to improve performance status and prolong survival in extracranial NSCLC [9–11]. Recently the effectiveness of TKIs in central nerve system (CNS) metastases from NSCLC has also been demonstrated [12,13]. Remarkable response and mild toxicity to EGFR TKI treatment makes itself an attractive option for patients with BM from NSCLC. We here present a review about the use of EGFR-TKIs in this context and the following questions would be discussed: Are TKIs capable of permeating across BBB? How to increase the concentration in cerebrospinal fluid to overcome the resistance of refractory metastases? Would the combination with other treatment like radiotherapy bring about advanced effect? And which patients with BM is the fittest population to EGFR-TKI treatment?

## The capability of permeating across blood–brain barrier

In general, primary brain neoplasms and BM are resistant to systemic chemotherapy [14] and this resistance has been attributed to the inability of drugs to cross BBB [15]. The BBB is formed by tight junctions between brain endothelial cells and its physiological

* Corresponding author. Tel.: +86 531 67626142; fax: +86 531 67626141.
*E-mail address:* mengxue5409@126.com (X. Meng).

http://dx.doi.org/10.1016/j.canlet.2014.04.019
0304-3835/

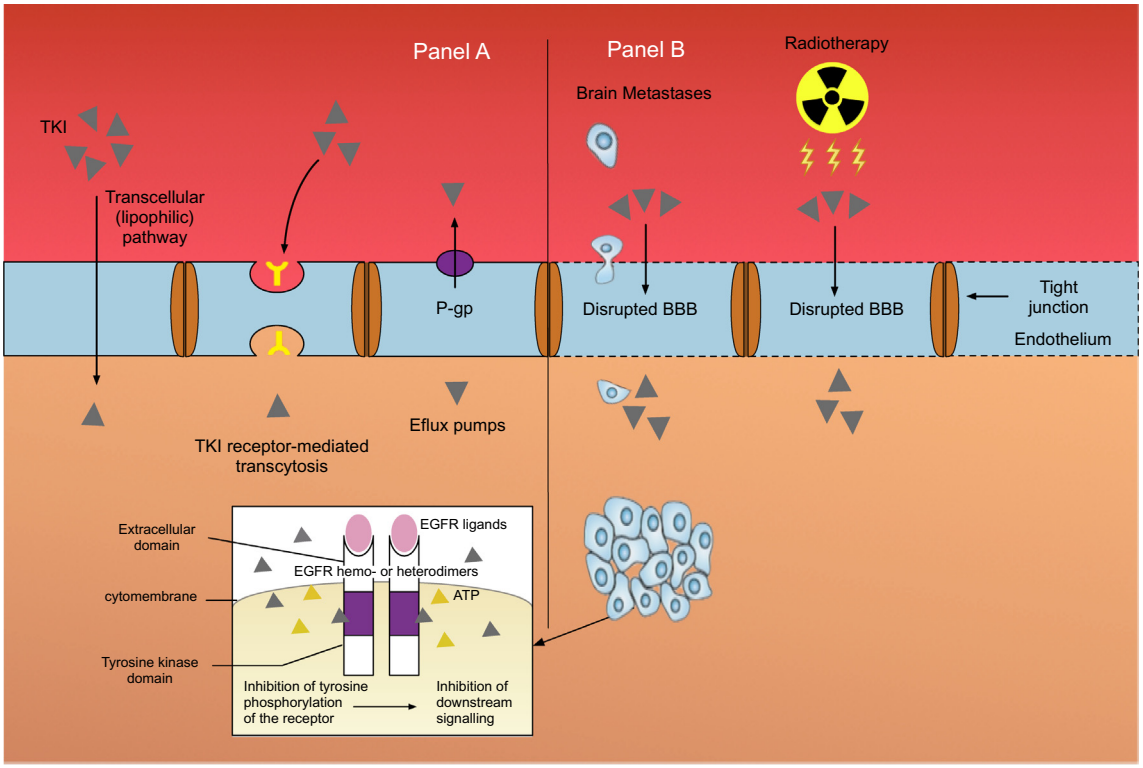


**Fig. 1.** The capability permeateing across blood-brain barrier (BBB). Panel A: BBB is formed by endothelium cells which are connected by tight junction. This structure severely limits lipophilic passive pathway of TKIs into the central nerve system. Receptor-mediated active transport mechanics allow entry for limited concentrations of TKIs and are counteracted by P-pg which is one of efflux pumps located on membrane of endothelium cells. The mechanism of TKI's action on cancer cells is also be presented. Panel B: Brain irradiation and metastasis would disrupt BBB and lead to an increased passive pathway of TKIs.

function is to maintain brain homeostasis by excluding toxic metabolites from the brain. Large hydrophilic molecules such as chemotherapeutic drugs can only be transported across the membrane by receptor-mediated mechanisms [16]. In contrast to traditional cytotoxic agents, the capability of TKIs to permeate across BBB is certain and has been demonstrated lively. In a case report, accumulation of $^{11}$C-erlotinib in the BM was visualized by positron emission tomography in a EGFR-mutant NSCLC patients [17]. Ideal characteristics of compounds with a higher probability of crossing the BBB include a low molecular weight, a non-polar nature, and not being substrates for efflux pumps [18]. However, even with small molecular weight, the ability of erlotinib and gefitinib to permeate into cerebrospinal fluid seemed limited. Reported by case series and small sample study [19–22], only a small fraction of the plasma levels could be achieved in cerebrospinal fluid at standard doses. And the inoperative exposure within CNS plays an important role in the refractory condition of BM to TKIs despite control of extracranial disease in EGFR-mutant NSCLC. Moreover a preclinical study concluded that gefitinib is a substrate to P-glycoprotein (P-gp) which is one of efflux pumps and is associated with multiple drug resistance mechanisms of brain tumors [23]. During the BM process the integrity of BBB would be damaged so the penetration ability of TKIs to CNS with metastases could be improved [24]. Indeed the hypothesis was confirmed, however, the effect was limited [20] (Fig. 1).

Surprisingly, the impenetrability of BBB also play a positive role in BM. Because of inadequate drug penetration into the cerebrospinal fluid (CSF) across a relatively intact BBB, the CNS metastases might be still without secondary resistance mutations, despite the concurrent acquisition of resistance mutations outside the CNS. And given autopsy indicating the discordance [25–27], Jackman et al. [28] described that patients who experience isolated CNS failure would not be considered as having systemic acquired resistance to EGFR TKI therapy. In other words, with efficient manners to achieve adequate concentration within CNS, intracranial metastases could be improved by tyrosine kinase inhibitors.

## To boost cerebrospinal fluid exposure in refractory metastases

As discussed above, administration of TKI at standard dosage may be helpless to refractory and relapsing BM due to failing to provide adequate concentration in CSF. In order to boost TKIs' exposure in CSF, plenty of extra strategies have been explored.

### *Dose escalation*

While erlotinib and gefitinib at routine dosage hardly achieve satisfactory CSF permeation, dose escalation of EGFR-TKIs would improve the exposure within CNS and relieve the resistance to standard-dose inhibitors in BM from EGFR-mutant NSCLC. In a case report, Jackman and his colleagues present a patient with EGFR-mutant metastatic NSCLC receiving gefitinib [26]. The patient developed BM despite control of his extracranial disease and was treated with WBRT while continuing with gefitinib at standard dosage of 250 mg/day. With repeated episodes of CNS progression, gefitinib was further increased to a maximum dose of 1000 mg/day. With each increase in gefitinib dose, CSF concentration was increased correspondingly and the patient responded radiographically and symptomatically. With gefitinib administered at such high dose, the patient began to demonstrate somnolence and rising hepatic transaminases leading to a decreased dose of 500 mg/day. Postmortem examination of the tumor cells from five metastatic sites were conducted after his death and all of the tumours from