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Review

Treatment options for EGFR mutant NSCLC with CNS involvement—Can patients BLOOM with the use of next generation EGFR TKIs?

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ABSTRACT

With the use of EGFR TKIs, patient survival is now prolonged and as a consequence, a higher chance of development of CNS metastases has been observed during the course of the disease. CNS metastases remains a therapeutically challenging subset of patient to treat owing to the blood-brain barrier (BBB). Prior to routine EGFR mutation testing, surgical resection, stereotactic radiosurgery and/or whole brain radiation therapy (WBRT) were the main treatment options whereas treatment options for patients with leptomeningeal metastases (LM) included intra-thecal chemotherapy, WBRT, and ventriculo-peritoneal shunting. Unfortunately outcome for both BM and LM remains poor with median survival between 3 and 6 months. Systemic treatment with EGFR TKIs had been effective in the treatment of intracranial metastases but efficacy of early generation TKIs were hampered by its limited BBB penetration. The next generation EGFR TKIs osimertinib and AZD3759 have improved BBB penetration and the BLOOM study of osimertinib and AZD3759 has reported highly promising intracranial efficacy and may herald a new frontier to treat this therapeutically challenging subset of advanced EGFR mutant patients.

Contents

1. Introduction

Lung cancer remains a leading cause of death worldwide and the majority of the non-small-cell lung cancer (NSCLC) is diagnosed in the advanced stage [1]. Brain metastases (BM) and leptomeningeal metastases (LM), are frequent sites of progression, accounting for

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10–15% at the time of diagnosis and 30–50% cumulatively throughout the course of the disease [2–4]. Central nervous system (CNS) metastases can cause significant morbidity including neurological deficits, reduced quality of life and poorer survival with a median survival of 4–6 months [5,6].

The treatment landscape of NSCLC had undergone a paradigm shift with the discovery of activating epidermal growth factor receptor (EGFR) [7] and subsequent trials have shown EGFR tyrosine kinase inhibitors (TKIs) to be superior to chemotherapy in terms of objective response rate (ORR), progression free survival (PFS) and quality of life [8–10]. With the use of EGFR TKIs, patient survival is now prolonged and as a consequence, a higher chance of development of brain metastases has been observed during the course of the disease. In a study of NSCLC patients without baseline brain metastases, CNS progression occurred at a rate of about 50% at 3 years [11]. The effect of EGFR-TKI and NSCLC *EGFR* mutation status on the risk of CNS progression has been published with conflicting results. In a study of patients with advanced NSCLC and somatic EGFR mutations initially treated with gefitinib or erlotinib, the 1- and 2-year cumulative risk of CNS progression was 7% and 19%, respectively [4]. In a larger study, the one and two year cumulative risk of CNS progression was 6%, and 21% in the EGFR-TKI group versus 19%, and 32% in the chemotherapy group [12]. One limitation of these two studies is the risk of CNS progression was not independently examined in a NSCLC cohort without EGFR mutations, thereby limiting the ability to evaluate a possible altered biologic predisposition of *EGFR* mutated lung cancer for CNS sites.

Whilst the systemic efficacy of EGFR TKIs has been well established, its activity in intracranial disease has, until recently, been less well established [13]. Patients with active or untreated CNS metastases are often excluded from the NSCLC clinical trials leading to the limited data in this patient subpopulation. Some early phase and retrospective data have reported activity of EGFR TKIs in CNS metastases, either as monotherapy or as part of multi-modality approach. Thus this is an area of unmet clinical need and new therapeutic approaches are warranted [4,14–16].

This review article aims to review the current strategies in the management of patients with EGFR mutant NSCLC with CNS metastases or LMD with a focus on EGFR TKIs, and in particular, a new generation of EGFR TKI with potentially higher CNS activity.

2. Brain metastases and blood brain barrier (BBB)

The CNS is shielded by BBB and is considered a pharmacologic sanctuary site. The successful treatment of CNS metastases would need to take into account individual drug pharmacokinetics as the majority of drugs are substrates for the drug efflux transporters P-glycoprotein (P-gp) and breast cancer-resistance protein (BCRP). These transporters are highly expressed in the BBB and actively remove drugs including chemotherapy from CNS [17,18]. In addition, some chemotherapeutic agents and monoclonal antibodies are unable to cross the BBB due to its large molecular weight [19]. These mechanisms lower the concentration of drugs in the CNS and consequently these agents were unable exert its anti-tumour activities resulting in lower efficacy intracranially [20,21]. The level of plasma and CSF of the first and second generation EGFR TKIs are summarised in Table 1.

At diagnosis, there is a high concordant rate of 86–100% of EGFR mutations in the primary, extracranial metastases and brain metastases [22–24]. After a period of treatment of EGFR TKIs, there is a discordant rate of acquired resistance mechanism between intracranial and extracranial metastases. The frequency of commonest acquired mechanism of resistance systemically, T790M mutation, has been noted to be lower in brain metastases. In a study of 78 EGFR mutant patients who had undergone rebiopsy after TKI failure, only 17% of CNS lesions were T790M mutated compared to 41% in systemic lesions [25]. This illustrated the selection pressure may be lower intracranially owing to the lower EGFR TKI concentration in cerebrospinal fluid (CSF) compared to serum concentration [21,25].

3. Treatment strategies for EGFR mutant NSCLC with brain metastases

Several strategies are available to treat NSCLC patients with *EGFR* mutant with CNS metastases including the use of local therapy such as surgical resection, stereotactic radiosurgery (SRS) or whole brain radiotherapy (WBRT) and the use of systemic therapy such as chemotherapy and EGFR TKIs (Table 2). More recently, there has been interest in using immune checkpoint inhibitors in patients with advanced NSCLC with brain metastases.

3.1. Local therapy with either surgery, stereotactic radiosurgery and/or whole brain radiation

Surgical resection could be considered for patients with oligo brain metastases in locations amenable for resection. Even if surgery was possible, the treating physicians would need to take into consideration the patient's performance status, comorbidities, potential loss of neurological functions and the extent of systemic disease before proceeding with surgical resection. Only a small number of patients would qualify and benefit from CNS metastasectomy [26].

Stereotactic radiosurgery (SRS) is the delivery of high-dose radiation to CNS metastases with minimal radiation dose to surrounding tissue thus minimizing the sequelae of radiation to brain parenchyma. This is achieved by using multiple convergent beams. SRS had been studied in several retrospective and randomized trials yielding a median overall survival of around 8–9 months [27–29]. SRS would also be considered for lesions that are not amenable for

Table 1
Summary of plasma, CSF and CSF: plasma ratio levels for erlotinib, gefitinib and afatinib.

Patient sample size	Dose	CSF (nM)	Serum/plasma (nM)	CSF:plasma ratio	Reference
Erlotinib					
1	1500 mg weekly	130 nM	1,1300 nM	1.15%	[70]
3	150 mg daily	34.7–186 nM	1163–3210 nM	2.5–13%	[71]
9	150 mg daily	66.9 nM	2653 nM	2.77%	[72]
Gefitinib					
1	500 mg daily1250 mg daily	6.2 nM39.4 nM	NR 3730 nM	NR 1.05%	[21]
8	250 mg daily	8.2 nM	729 nM	1.13%	[20]
22	250 mg daily	13.87 nM	1100 nM	1.3%	[73]
Afatinib					
1	50 mg daily	1.04 nM	149.25 nM	0.69%	[74]

CSF = cerebrospinal fluid; nM = nanomolar, NR = not reported.