CHAPTER 8A

High-dose, pulsatile erlotinib in two NSCLC patients with leptomeningeal metastases – one with a remarkable thoracic response as well

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ABSTRACT

A considerable number of patients with epidermal growth factor receptor (EGFR)-mutated non-small-cell lung cancer (NSCLC) develop leptomeningeal metastases. Leptomeningeal metastases are associated with deterioration of clinical symptoms and poor survival. Traditionally, treatment of metastases in the central nervous system consists of radiotherapy and less frequently, surgery. The role of systemic therapy is limited due to the blood-brain barrier inhibiting pharmacological doses to be reached in the central nervous system. Several case reports have described high-dose, pulsatile tyrosine kinase inhibitors as an effective treatment of leptomeningeal metastases, based on the hypothesis that higher concentrations in the cerebrospinal fluid can be reached by higher systemic concentrations. Here, we describe two patients with EGFR-mutated non-small cell lung cancer, with both clinical and radiological response to this high-dose, pulsatile regimen. Interestingly, one patient showed a remarkable response of intrathoracic response as well.
INTRODUCTION

EGFR-mutated NSCLC is associated with a favourable prognosis, high rate of response to EGFR-TKI’s and consequently improved overall survival when compared to other subtypes of NSCLC. However, after an initial response to EGFR-TKI’s, progression of disease is inevitable. A substantial number of patients develop central nervous system (CNS) metastases, in some series up to 30%. CNS metastases are associated with disabling neurological symptoms, deterioration of performance status and poor survival. Traditionally, treatment of CNS metastases consists of radiotherapy and in selected cases, surgery. Systemic treatment is believed to have a limited role, due to the blood-brain barrier (BBB). Since EGFR TKI’s are a substrate of P-glycoprotein, the BBB is preventing pharmacological dose of EGFR TKI’s at standard dosing regimes to be reached in the CNS. Due to this lower drug concentration, selective pressure in the CNS is different and acquired resistance mechanisms that are often demonstrated in metastases outside the CNS are believed to be less common in CNS metastases. Hence, these metastases would still be sensitive to EGFR-TKI-treatment, if only sufficient penetration of these drugs into the CNS could be achieved. Theoretically, administering TKI’s in a higher dose could achieve higher concentrations in the cerebrospinal fluid. This strategy has been applied before, with encouraging results (1-6). Here, we report two EGFR-mutated NSCLC-patients with leptomeningeal metastases successfully treated with high-dose, weekly erlotinib, one with a remarkable response of intrathoracic disease as well.

Case 1

A 49-year old, Creole female underwent a lobectomy of the left upper lobe in 2006 because of adenocarcinoma followed by adjuvant radiotherapy. In 2009 a local recurrence was diagnosed and mutational analysis showed an EGFR mutation exon 21 (L858R). She was treated with erlotinib on which she maintained stable disease for twelve months. In 2010 she developed single-site progression of a left supraclavicular lymph node. Biopsy revealed adenocarcinoma, with weak detection of the former L858R mutation, for which she was treated with radiotherapy (5x5Gy) while erlotinib therapy was maintained. In November 2011, a gastroduodenoscopy was performed because of persistent, progressive pain in the upper abdomen and evident compression of the proximal duodenum was observed. A CT abdomen revealed a big retro- and intraperitoneal mass. Because of the clinical situation and the high suspicion of abdominal metastasis, chemotherapy consisting of pemetrexed and cisplatin at standard dose, was initiated before pathological confirmation was obtained. One month later, she experienced headache and vomiting. MRI-cerebrum showed diffuse leptomeningeal metastases (Figure 1a). Erlotinib pulsatile therapy was started at a dose of 1000 mg once a week in conjunction with chemotherapy, which was increased to 1500 mg once a week after the first dose. This treatment regimen was well tolerated. Side effects
were mild malaise on day of taking the high dose and skin toxicity grade 1. Follow-up MRI-cerebrum demonstrated evident response of the leptomeningeal metastases (Figure 1b) and months after initiation of high dose erlotinib, she remains free of neurological symptoms. Follow-up CT-scans showed control of both intrathoracic and intra-abdominal disease as well.

Case 2
The second patient is a female patient of 51 years old diagnosed with stage IV NSCLC in 2008. An \textit{EGFR} mutation was detected in exon 19 (del 747-752 (P753S)). She has been treated with erlotinib in combination with sorafenib, single agent erlotinib and afatinib in combination with cetuximab chronologically. After progression on the latter regimen in March 2012 she was treated with 2 cycles of cisplatin and pemetrexed at standard dose. A CT-scan showed stable disease of the intrathoracic lesions (Figure 3a-b) but she developed neurological symptoms. An MRI-scan showed leptomeningeal metastases (Figure 2a) pathologically confirmed by lumbar puncture from which an identical activating exon 19 mutation was detected. She was then treated with erlotinib 1500 mg once weekly and cytotoxic chemotherapy was continued. Surprisingly after 3 weeks of treatment with the high dose erlotinib regimen there was significant decrease of the intrathoracic disease (Figure 3c). The neurological symptoms improved drastically, confirmed by an MRI-cerebrum that showed decrease of leptomeningeal metastases (Figure 2b). At time of writing, she is still on erlotinib pulsatile therapy and chemotherapy.

DISCUSSION
Up to one third of \textit{EGFR}-mutated NSCLC patients develop metastases in the CNS after initial successful treatment with an EGFR-TKI. Forty percent of these CNS metastases are leptomeningeal metastases (7). Whereas leptomeningeal metastasis in \textit{EGFR}-wild type NSCLC is associated with a dismal prognosis with a median survival of 3-4 months, median survival in \textit{EGFR}-mutated NSCLC patients with leptomeningeal metastases is 7-14 months (8, 9). Often, leptomeningeal metastases are diagnosed while other disease sites are still in remission. Due to different selection mechanisms, resistance mutations that are frequently encountered in the primary tumour and systemic metastases, are not demonstrated in synchronous or metachronous CNS metastases (10-12). Theoretically, these metastases would still be sensitive to TKI-therapy, however, due to the blood-brain barrier; intrathecal drug concentrations from standard doses EGFR-TKI’s in the CNS are much lower than systemic concentrations (6, 13). As illustrated in these two cases, therapeutic concentrations of TKI’s in CSF can be achieved by pulsatile, weekly, high-dose erlotinib. It has been demonstrated that erlotinib up to doses of 2000 mg weekly is tolerable and toxicity is manageable (14). Side
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effects of the high, weekly dose schedule are similar to the daily standard schedule; mainly rash, diarrhoea, nausea and fatigue. Grade of toxicity is usually mild; in a study evaluating nine patients, no grade ≥3 toxicities were observed (3). As other therapeutic options are lacking for this category of patients, this treatment schedule could be considered in EGFR-mutated patients with leptomeningeal metastases. Results from prospective trials are awaited for.

Evidence of adding EGFR-TKI’s to chemotherapy is controversial. While the initial phase III studies combining cytotoxic chemotherapy with EGFR-TKI’s were negative (15, 16), recent randomized phase II and phase III studies found a significant survival benefit both in unselected (17) and selected (18) patients. In the described patients, the administration of chemotherapy (directed towards extracerebral lesions) and pulsatile erlotinib (directed towards CNS-lesions) simultaneously proved to be an effective treatment strategy.

In the second patient, an MRI-cerebrum confirmed partial response of leptomeningeal metastases after pulsatile erlotinib therapy. Interestingly, thoracic disease in this heavily TKI-pretreated patient responded evidently to the high-dose, pulsatile regimen as well, while response to recent chemotherapy was stable disease at best. Several acquired resistance mechanisms have been identified, for example the T790M mutation and MET-amplification. However in approximately 30% the underlying resistance mechanism remains indistinct (19). Tissue from the thoracic lesions for pathological analysis was not obtained, precluding a molecular explanation for the radiological response. Nevertheless, it is known that for example the T790M mutation increases the affinity of the EGFR tyrosine kinase for ATP, thereby restoring signal transduction through this pathway. By increasing plasma concentrations of erlotinib, which is a competitive inhibitor of EGF signalling, sensitivity of EGFR for erlotinib might theoretically be restored.

If high-dose pulsatile erlotinib were effective in patients experiencing systemic progression of disease while on EGFR-TKI treatment, this would provide a new and relatively uncomplicated treatment potential in this category of patients lacking therapeutic opportunities. A prospective trial is planned, evaluating the effect of high-dose, weekly erlotinib on systemic progression of disease after treatment with standard doses EGFR-TKI in EGFR-mutated NSCLC patients.

Informed consent of both patients was acquired.
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REFERENCE LIST


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Figure 1 and 2
1a: Axial contrast-enhanced T1-weighted MRI-cerebrum shows widespread contrast enhancement of leptomeninges suspect for leptomeningeal metastases.  
1b: Follow-up axial contrast-enhanced T1-weighted MRI-cerebrum shows decreased contrast enhancement of leptomeninges, suggesting response of leptomeningeal metastases.  
2a: Axial contrast-enhanced T1-weighted MRI-cerebrum shows widespread contrast enhancement of leptomeninges suspect for leptomeningeal metastases.  
2b: Follow-up axial contrast-enhanced T1-weighted MRI-cerebrum shows decrease contrast enhancement of leptomeninges, suggesting decrease of leptomeningeal metastases.

Figure 3
Serial Thoracic CT scans at progression:
- after afatinib-cetuximab combination therapy (A)  
- after 2 courses of polychemotherapy (cisplatin-pemetrexed) (B)  
- after 3 courses of pulsatile erlotinib (C)