Tumoral hemorrhage of brain metastasis from non-small cell lung cancer after gefitinib therapy: two case reports and literature review

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Abstract

**Background:** Gefitinib is one of small molecule inhibitors of epidermal growth factor receptor tyrosine kinase (EGFR TKIs). Clinical trials have demonstrated that it is effective in the treatment of a subset of patients with advanced non-small cell lung cancer (NSCLC). It has also been regarded as a relatively safe agent, and in addition to a small proportion of fatal interstitial pneumonia, the common adverse drug reactions of gefitinib are diarrhea and skin rash, which are generally mild and reversible. Herein, we report the first two cases of brain hemorrhage that might be involved in the use of gefitinib.

**Case presentation:** In our report, two patients with brain metastasis from NSCLC are described to develop brain hemorrhage after gefitinib therapy. The hemorrhage in one case occurred one month after gefitinib combined with whole brain irradiation (WBRT), and in another case it developed slowly with a brain metastasis 8 months after gefitinib monotherapy for diffuse pulmonary metastasis from a previously operated lung cancer.

**Conclusion:** We speculate brain hemorrhage as possible adverse drug reaction of gefitinib with NSCLC and suggest that the clinicians be aware of this presumably rare entity. More data are needed to confirm our findings, especially when gefitinib is used in settings of brain metastases either from NSCLC or other origins.
Background

Gefitinib is one of the inhibitors of epidermal growth factor receptor tyrosine kinase (EGFR TKIs), designed to offer targeted therapies for a variety of solid tumors including the lung cancer [1]. Clinical trials have demonstrated that gefitinib is effective or non-inferior to chemotherapy in the treatment of a subset of patients with advanced non-small cell lung cancer (NSCLC) [2-4]. Gefitinib has also been regarded as a relatively safe agent, with the most common adverse drug reactions being diarrhea and skin rash, which are generally mild in nature and reversible [5, 6].

Here we describe two cases of brain metastasis from NSCLC who developed brain hemorrhage after gefitinib therapy. To our knowledge, they are the first reported cases of brain hemorrhage that might be involved in the use of gefitinib. Recently, a few hemorrhagic events in other parts of the body have also been reported after gefitinib administration [7-9]. Thus, we speculate brain hemorrhage as possible adverse drug reaction of gefitinib with NSCLC and suggest that the clinicians be aware of this rare entity. More data are needed to confirm our findings, especially when gefitinib is used in settings of brain metastases either from NSCLC or other origins.
CASE PRESENTATION

Case one:

A 52-year-old male, who was an ex-smoker with a smoking history of ten years, was found a solitary pulmonary nodule (SPN) in the upper lobe of right lung by CT scans 6 years ago. He refused surgery or any invasive procedures to the nodule, so chest CT scan was performed every six months for follow-up. Then in May 2009 the SPN increased in size with multiple lung and ribs metastasis by CT examination (Fig.1 A). Brain MRI also showed multiple metastatic lesions with the largest one in the left occipital lobe (Fig.2 A). CT-guided percutaneous needle biopsy of the pulmonary lesion proved adenocarcinoma. After refusing to receive chemotherapy with toxic agents, he began to take gefitinib at a daily dose of 250 mg as first-line treatment for NSCLC combined concurrently with whole brain irradiation (WBRT) for the metastatic brain tumors. WBRT was performed to a total dose of 30 Gy with a fraction size of 3 Gy over 2 weeks. During the treatment, mild skin rash and nausea and vomiting were observed and all these side effects were well tolerated. One month later, chest CT showed significant shrinkage of the primary lesion and marked absorption of pulmonary metastases (Fig.1 B). Meanwhile, because the patient began to feel recurrent headache and nausea, brain MRI demonstrated a left occipital lobe mass that was consistent with a subacute hematoma (Fig.2. B). The platelet counts and prothrombin time and activated partial thromboplastin
time of the patient were within normal ranges. The patient had no history of diabetes or hypertension or coagulation disorders, and during hospitalization he had no history of trauma. Except for mild to moderate headache and nausea, the patient complained of no other discomfort such as impaired orientation to person and place, hemidysesthesia or hemiopia. So he was discharged from hospital after one week’s supportive treatment with mannitol and methylprednisolone.

Case two:

A 75-year-old male, an ex-smoker too, was diagnosed right lung cancer in July 2007, and underwent operation on 27th July 2007 after routine staging procedures. The pathology was adenocarcinoma with positive margins and ipsilateral hilar and mediastinal lymph node metastasis (Stage pT3N2M0). So postoperative adjuvant chemotherapy and thoracic radiotherapy (59 Gy/32 fractions) were performed. The patient was well tolerant to the therapy and without evidence of disease until July 2008, when CT scans demonstrated diffuse pulmonary dissemination (Fig.3 A) and a right hepatic metastasis. The patient started taking gefitinib at a daily dose of 250 mg, and CT scans about 2 months later showed near-CR (Complete Response) of the pulmonary lesions (Fig.3 B). After five months’ medication of gefitinib, the patient developed severe bilateral paronychia. So he had an operation of nail arrachement on 11th November 2008. In March 2009, the patient felt right limb numbness with unstable walking. Brain MRI indicated
a metastatic tumor in the left thalamus with intratumoral hemorrhage (Fig.4). The platelet counting of the patient was 143,000/mm³ and there were no other underlying disorders that might be related to the brain hemorrhage. WBRT was recommended but the patient preferred watchful waiting for minor discomfort. On 5th June 2009, more metastatic lesions (smaller but also with evidence of bleeding) were found on brain MRI and subsequently WBRT (30 Gy/15 fractions) was performed on the patient. The patient now is still alive with mild right hemiparesis.

Discussion

Epidermal growth factor receptor (EGFR) is a member of the HER tyrosine kinase growth factor receptor family that signals cellular differentiation, proliferation, invasion, metastasis, and survival. It is expressed in a variety of human cancers including NSCLC (40%-80%), colorectal cancer (25%-77%), pancreatic cancer (30%-50%), breast (15%-30%), ovarian (35%-70%), prostate (40%) and gastric (33%) cancers [1]. Among the above cancers, NSCLC was one of the most frequently studied objects of EGFR-targeted therapy, as evidenced by clinical trials such as INTEREST, ISEL (for gefitinib), and BR21 and SATURN (for erlotinib, another EGFR-TKI) [2, 4, 11, 12].

Gefitinib (ZD1839, Iressa), a selective inhibitor of EGFR tyrosine kinase (EGFR-TKI) which is competitive with the combination of EGFR tyrosine kinase, acts through blocking the signal transduction pathway of epithelial
growth factor and thereby inhibiting the proliferation and metastasis, and, promoting the apoptosis of tumor cells [1]. The orally administered gefitinib has achieved a great effect since its approval by FDA in 2003, for it has less toxicities compared with traditional cytotoxic chemotherapy. In addition to an extremely small number of fatal interstitial pneumonia reported [12], the common adverse drug reactions of gefitinib are diarrhea, skin rash, dry skin, nausea and vomiting. On most occasions these reactions are mild and reversible. Other adverse effects are less common, like pruritus, anorexia, asthenia and weight loss [13]. For all the above reasons, gefitinib has been used as the third or second line therapy for advanced and metastatic NSCLC, or even evaluated as the first line therapy (IPASS trial) for a subset of patients with NSCLC [14], like our first case who took gefitinib without any previous cytotoxic therapies.

Targeted therapies also aim at other signal transduction pathways like vascular endothelium growth factor (VEGF). It is well known that anti-angiogenic therapy (AAT) can lead to serious hemorrhagic events in NSCLC, particularly in those of squamous cell origin [15]. An early phase I trial of bevacizumab, an anti-VEGF monoclonal antibody, also detected a case of intracranial hemorrhage from a choriocarcinoma brain metastasis, so patients with brain metastasis are not candidates to AAT. On the other hand, anti-EGFR therapy has not been warned against increased risks of bleeding, except a few case reports of anecdotal experience.
There has been a case report in which severe alveolar hemorrhage occurred after four weeks’ gefitinib therapy in a 56-year-old man of NSCLC in Japan [9]. Recently, another two reports on bilateral subdural hemorrhage (SDH) after oral gefitinib have been published [7-8]. In one, a 75-year-old woman was diagnosed as stage IV NSCLC and was introduced to take gefitinib at a daily dose of 250 mg. About 7 months later, the patient gradually developed headache and weakness, and CT demonstrated bilateral SDH another 2 months later. The authors thought that bilateral SDH might be resulted from obstruction of dural vessels by latent dural metastasis and was also suggested as a possible adverse event of gefitinib therapy. Huang et al reported another case in which a 57-year-old male developed bilateral SDH after WBRT combined with EGFR-TKIs for NSCLC with brain metastases. Gefitinib was replaced with erlotinib on the 5th day after WBRT. During a follow-up period with erlotinib alone after completing WBRT, the patient developed bilateral SDH. The authors did not make a clear explanation for the complication.

Apart from the above reports of hemorrhagic events that might be related to gefitinib in NSCLC, there was also a recent phase III study showing gefitinib dose-dependently increased tumor hemorrhage–type events in recurrent squamous cell carcinoma of the head and neck [16].

In our report, two patients developed brain hemorrhage after taking gefitinib. Though in our first case brain tumor hemorrhage developed one month after
a combination of gefitinib and WBRT, we still thought gefitinib might had taken a role. In the first place, comorbiditis such as thrombocytopenia, coagulation abnormalities or other underlying cerebrovascular diseases or head trauma had been excluded. Secondly, our experience and reports from others suggested that WBRT alone was unlikely to be the cause of tumoral hemorrhage of brain metastases, or rather could decrease the hemorrhagic events through blunting angiogenesis and normalizing tumor vasculature [17-18]. As gefitinib may be a radiation sensitizer in the treatment of radiation therapy in a variety of tumors, including NSCLC, head and neck, breast, and colorectal, and enhance the antitumor efficacy of radiation therapy [19-20]. We think it may strengthen the role of radiotherapy induced vascular occlusion and subsequent post-ischemic hemorrhage. We also speculate that gefitinib in combination with WBRT might lead to rapid shrinkage of brain metastasis and avascular necrosis, induce reconstruction of microvasculature and vascular abnormality, subsequently leading to tumoral bleeding. Though in a research on treatment of brain metastasis from NSCLC with WBRT and gefitinib showed that acute side effects were generally well tolerated, and no phenomenon of hemorrhage were found in their research [6]. We still suspect gefitinib may be responsible in our case for the hemorrhage.

In the latter case, hemorrhagic brain metastasis was found 8 months after gefitinib monotherapy. Before that, the patients also experienced severe
paronychia and underwent a nail arrachement 3 months after gefitinib administration. MRI showed evidence of both subacute (hyperintensities on T1-weighted image) and chronic (hypointensities on T2-weighted image) components of bleeding, with no obvious perilesional edema, which might account for the mild symptoms and signs of the patients. For the above reasons, the patient was not immediately performed WBRT until some new hemorrhagic metastases were detected in other parts of the brain. So whether the brain metastasis and tumoral hemorrhage were just coincidence or as a result of gefitinib therapy? As reported in the literature, the incidence of spontaneous brain metastasis hemorrhage from NSCLC seemed to be very low [21-22]. Furthermore, recent studies on EGFR inhibition with gefitinib also showed its influence on angiogenesis [23]. Since anti-angiogenic therapy (AAT) with bevacizumab has been reported to evoke hemorrhagic events, it seems logical that gefitinib might be involved in the tumoral hemorrhage of brain metastasis in our 2 cases.
Conclusion

In summary, from our cases and others reported in the literature, we speculate brain metastasis hemorrhage as possible adverse drug reaction of gefitinib with NSCLC and suggest that the clinicians be aware of this rare entity. More data are needed to confirm our findings, especially when gefitinib is used in settings of brain metastases either from NSCLC or other origins.
**Competing interests**

The authors declare that they have no competing interests.

**Consent**

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

**Authors’ contributions**

DFY analyzed the data and wrote the manuscript. JSY, XLS, and XBL made substantial contributions in data acquisition and data interpretation. SXY participated in study design and coordination. All authors read and approved the final manuscript.
References


Figures Legends

**Figure 1.** Before gefitinib therapy, chest CT scan showed a primary lesion (arrow) in the upper lobe of right lung and multiple pulmonary metastases (arrowheads) in both lungs (A). One month later with gefitinib therapy, chest CT scan showed significant shrinkage of the primary lesion (arrow) as well as marked absorption of pulmonary metastases (B).

**Figure 2.** Contrast-enhanced T1-weighted brain MRI showed multiple metastatic lesions, with the largest one (arrow) in the left occipital lobe (A). One month after gefitinib (two weeks after WBRT), T1-weighted MRI demonstrated a subacute hematoma (arrow) within the metastatic lesion (B).

**Figure 3.** Chest CT scans showed pulmonary dissemination (arrows) from a previously operated NSCLC in the right lung. A patchy shadow (arrowhead) representing radiation fibrosis was also observed (A). About 2 month later with gefitinib therapy, chest CT scan showed significant absorption of the lesions (B).

**Figure 4.** T1-weighted brain MRI showed a metastasis of heterogeneous signal intensities in the left thalamus (arrow). Components of hyper-signal intensities represented subacute hemorrhage (A). The lesion was also of heterogeneous signal intensities on T2-weighted images, with components
of hypointense hemosiderins representing old hemorrhage (arrow) (B). Contrast-enhanced MRI showed inhomogeneous enhancement of the lesion (arrow) (C).
Figure 3