Brain metastases in metastatic non-small cell lung cancer responding to single-agent gefitinib: a case report

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Brain metastases are a frequent finding in patients with non-small cell lung cancer (NSCLC). The present case reports the clinical course of a patient who was treated with gefitinib alone for progressive brain metastases after whole-brain irradiation treatment (WBRT). A 50-year-old women with primary stage IV NSCLC (bone metastases) developed brain metastases after 3 cycles of chemotherapy consisting of paclitaxel and carboplatin (CBDA). After completion of the WBRT, magnetic resonance imaging (MRI) indicated further progression. Two cycles of temozolomide and topotecan were applied; this was ineffective in preventing central nervous system progression. For symptomatic brain metastatic disease the patient received gefitinib as single-agent treatment. Within a few weeks of treatment there was an obvious clinical improvement. Follow-up of the brain 2 months after the start of treatment showed a decrease in both the size and number of brain metastases. Additional manifestations in the lungs and the skeletal system were re-assessed as stable disease during the treatment with gefitinib. Within 4 months of treatment there were no side-effects such as skin rash or any other systemic toxicity. Gefitinib may therefore have a role in the treatment of brain metastases from NSCLC. *Anti-Cancer Drugs* 16:747–749 © 2005 Lippincott Williams & Wilkins.

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Introduction

Central nervous system involvement is a common finding in patients suffering from non-small cell lung cancer (NSCLC). Compared to 20% clinically apparent brain metastases during the course of the illness, the incidence in autopsy studies is more than twice as high (44%) [1].

Whole-brain irradiation treatment (WBRT) is currently the standard therapy for patients with unresectable brain metastases, but the impact on survival is generally low, with a median survival of 5 months [2]. In contrast to the well-established WBRT, systemic treatment of brain metastases is not widely accepted. The limited efficacy of systemic chemotherapy for brain metastases is explained by the poor penetration of most cytotoxic agents into the CNS. However, there is evidence of a potential benefit of systemic chemotherapy for brain metastases in some studies [3–10].

Gefitinib (Iressa; AstraZeneca) is an oral selective epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor that blocks signaling through EGFR and HER2. Gefitinib has demonstrated an acceptable toxicity profile as well as promising efficacy for patients with various advanced solid tumors [11–14]. Gefitinib induced a response rate of 19% and a median survival of 8 months in the second-line setting for patients with advanced NSCLC [12]. A few case reports and some small phase I/II studies have demonstrated efficacy of gefitinib in the treatment of brain metastases from NSCLC [15–21]. Here, we report a patient with CNS progression responding to single-agent gefitinib.

Case report

A 50-year-old woman was diagnosed with primary metastatic NSCLC (bone metastases) in June 2004. The patient was started on a combination chemotherapy consisting of paclitaxel and carboplatin (CBDA). After the third cycle the patient was committed to our ward suffering from a myoclonic seizure. Immediate magnetic resonance imaging (MRI) of the brain confirmed the presence of multiple, bihemispheric brain metastases. The patient underwent WBRT (45 Gy). For the associated vasogenic edema, the patient initially received corticosteroid treatment (24 mg dexamethasone daily) as well as phenytoin for symptomatic seizures. After completion of the WBRT, MRI indicated further progression, and the patient received 2 cycles of temozolomide and topotecan. Treatment was tolerated well, but in November 2004 general disease progression and physical deterioration was noted. MRI of the brain detected a dramatic increase in the number and size of the brain metastases with moderate vasogenic

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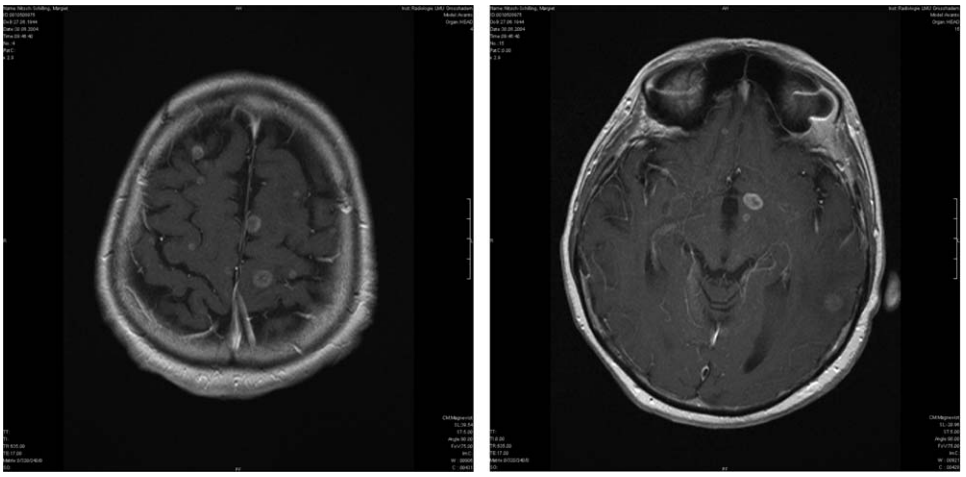
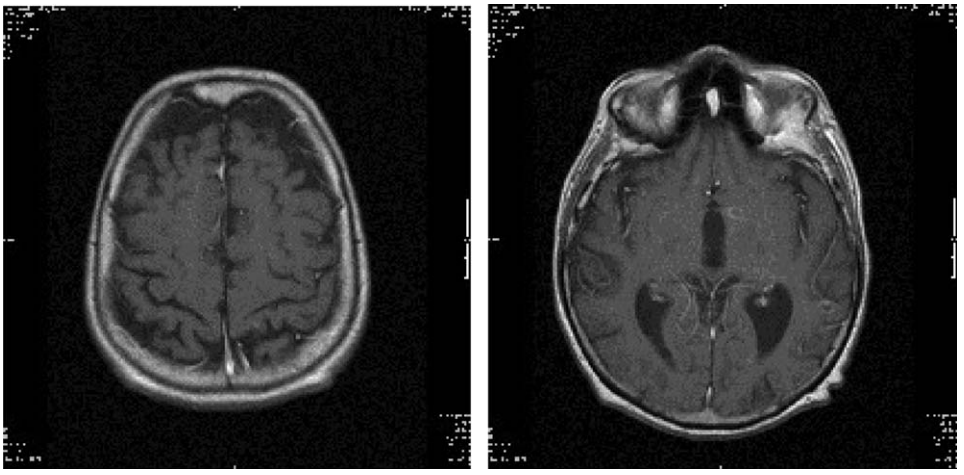
Fig. 1



MRI: CNS progression in November 2004 after WBRT and 2 cycles of temozolomide/topotecan.

Fig. 2



MRI January 2005: partial response to single-agent gefitinib after 2 months of treatment.

edema (Fig. 1). Peripheral manifestations assessed by computed tomography (CT) were considered to be stable. The patient was started on third-line gefitinib as single-agent therapy (250 mg orally daily), which was tolerated well. Except gefitinib and phenytoin, no further treatment was applied. The patient reconstituted physically within a few weeks of treatment.

When the patient returned for review of the MRI result on January 2005, she presented with a significantly improved physical condition. On MRI, all lesions showed a significant reduction in size and number with complete resolution of the associated vasogenic edema (Fig. 2). There were no side-effects such as skin rash or any other systemic toxicity.

Follow-up by CT in March 2005 showed a stable disease with respect to the primary tumor and the bone metastases.

Discussion

Brain metastases are common in patients with NSCLC. WBRT, the so-called 'gold-standard' for the treatment of brain metastases, is effective, but the impact on survival seems to be limited [2]. Despite some published responses to cytotoxic chemotherapy for brain metastases in NSCLC, the impact on long-term prognosis seems to be modest. There are few randomized trials comparing the addition of chemotherapy to surgery or WBRT. The trial of Nakawanga *et al.* reported prolonged median survival in patients who received platinum-based

chemotherapy after surgical resection of brain metastases for various solid tumors [22]. Robinet *et al.* failed to demonstrate a significant difference in both response and median survival in patients receiving early or delayed WBRT in addition to cisplatin and vinorelbine for brain metastases [9]. Finally, the addition of temozolomide to WBRT significantly improved the response rate, but not the overall survival [4]. Other single-agent and combination chemotherapies such as topotecan- and ifosfamide-based regimen have been shown to increase response rates, but there is still no evidence on their impact on survival.

Topotecan, a topoisomerase I inhibitor, has proven activity, with a response rate up to 58% against brain metastases in patients with simultaneous WBRT [23]. Temozolomide is also well established in the treatment of brain metastases from solid tumors [3,4]. The combination of both topotecan and temozolomide was given to the patient reported here after failure of the first-line treatment with paclitaxel and CBDA. The combination was well tolerated with moderate hematological side-effects, but disease stabilization was achieved only for a short period of 3 months duration, and clinical and imaging studies indicated rapid progression thereafter. In the absence of a standard treatment the patient was started on third-line, single-agent gefitinib.

Villano *et al.* published the first report of anti-cancer activity of gefitinib in brain metastases from NSCLC with a dramatic improvement of performance status after 2 months of therapy and objective responses on MRI [15]. There are several reasons for using gefitinib as treatment for patients with brain metastases due to NSCLC. The favorable toxicity profile of gefitinib, lacking myelosuppression, is especially appealing in patients with poor performance status [12]. In addition, the low-molecular-weight compound may penetrate the blood–brain barrier. This is supported by the clinical improvement and objective tumor response in our patient. In a comparable study by Chiu *et al.*, a response rate of 33.3% was reported. Interestingly, a significant correlation of response rate and associated skin rash was noted [19]. No skin rash occurred in our patient and other authors have also found responses without the occurrence of severe skin reactions [16].

Further investigation of gefitinib for brain metastases in solid tumors is warranted, and combined-modality therapy of gefitinib and radiotherapy in the management of brain metastasis remains to be investigated. Preclinical data suggested a radiopotentiating effect of gefitinib. Since local therapy has limited efficacy concerning disease control and prolonging overall survival, the role of systemic therapy continues to be explored. This new molecular-targeted therapy can penetrate the blood–brain barrier and induce a tumor response. Our observation justifies further investigation.

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