Med Oncol (2012) 29:2619–2622
DOI 10.1007/s12032-011-0148-x

SHORT COMMUNICATION

Prolonged activity of bevacizumab in adenocarcinoma of the lung with multiple brain metastases

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Received: 7 December 2011 / Accepted: 17 December 2011 / Published online: 31 December 2011

Abstract Patients with lung cancer having multiple brain metastases have poor outcomes. We present long-term disease treatment in a 60-year-old woman having greater than thirty brain metastases of NSCLC adenocarcinoma with a mutant allele of EGFR treated with differing chemotherapies including erlotinib, but disease response in the brain only with bevacizumab. Although initially restricted in use, increasing clinical reports have demonstrated safety of bevacizumab use in brain-involved cancer patients. Our case highlights that disease response to bevacizumab is similar in the brain to systemic disease and likely overcomes anatomical barriers that can limit other therapeutic agents.

Keywords Brain metastasis · NSCLC · Bevacizumab · MRI · CNS

Introduction

Bevacizumab is an angiogenesis inhibitor with FDA approval for multiple tumor types including colon [1], non-squamous non-small cell lung cancer (NSCLC) [2], kidney [3], and glioblastoma (GBM) [4]. The pivotal trials, except for GBM, excluded patients with brain metastases for concerns of intracranial hemorrhage. With FDA approval clinical use has advanced based on studies including a report on the incidental brain metastasis in thirteen randomized studies with bevacizumab that demonstrate cerebral hemorrhage risk is similar to non-bevacizumab-treated patients [5] and a prospective phase II clinical trial, AVF3752g (PASSPORT) [6]. This trial evaluated the safety of administering bevacizumab to 115 subjects with non-squamous NSCLC having treated brain metastasis. Bevacizumab was administered with concurrent chemotherapy agents or erlotinib in front-line or second-line therapy, and results demonstrate that bevacizumab was safe and had a low incidence of CNS hemorrhage. This has led to NCCN guideline changes to include use of bevacizumab in patients with treated brain metastasis [7].

We present a case of NSCLC where the addition of bevacizumab provides significant and enduring clinical benefits to brain metastases.

Case history

A 60-year-old woman was diagnosed with metastatic NSCLC after presentation with transient aphasia and headaches in July, 2009. She worked as a nurse and had a history of basal cell skin carcinoma and benign breast nodules. Chest imaging demonstrated a large mass in the left upper lobe, multiple bilateral pulmonary metastases, and involvement of thoracic vertebral bodies (Fig. 1a). Brain imaging showed us that enhancing masses consistent with metastases were found in multiple lobes of the brain [Fig. 2a, c, e, which includes axial T1-weighted (T1W) post-Gadolinium contrast MRI, T2W Flair, and diffusion-weighted images (DWI) b1000, respectively]. There were more than thirty lesions. The results of a bone scan were consistent with widespread metastatic disease, involving

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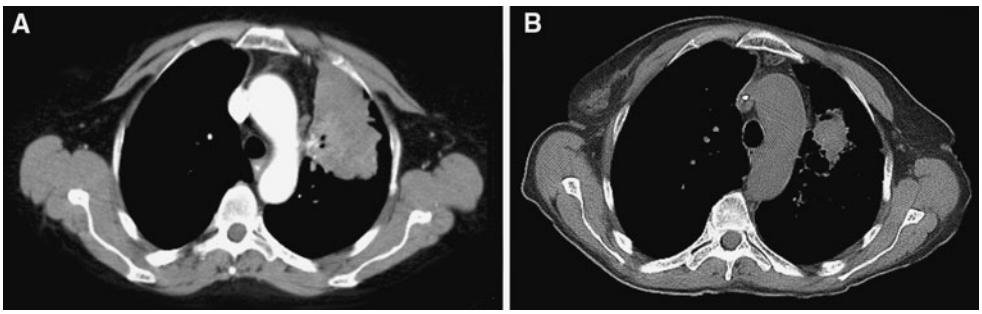

Fig. 1 **a** CT scan with IV contrast at diagnosis demonstrating a large spiculated and lobulated mass in the left hilar region and left upper lobe, with encasement of local structures. **b** CT scan without IV contrast, secondary to chronic renal insufficiency, demonstrating partial response to treatment, performed 2 years from diagnosis

multiple ribs, thoracic spine, and both scapulae and right femur. Pathology samples from bronchoscopy confirmed mucin-producing adenocarcinoma of a lung primary. Immunohistochemistry studies confirmed her diagnosis; positive reactivity for cytokeratin (CK) 7, thyroid transcription factor (TTF)-1, BER-EP4 and high-molecular-weight CK (HMWCK), and negative results for CK 20 and P63. She was initially treated with dexamethasone while receiving whole-brain radiation therapy (WBRT) (3,000 cGy, 10 fractions).

She then developed focal motor seizures and was managed with phenytoin and levetiracetam. After receiving WBRT and dexamethasone taper, doublet chemotherapy of cisplatin and docetaxel were administered on a 3-week cycle for four cycles. Zoledronic acid was also given to help with her bone metastases. Re-evaluation imaging demonstrated an increase in the size of pulmonary metastases. An MRI of the brain showed no significant change in the size of the enhancing portion of brain metastases but did have an increase in the vasogenic edema as evidenced from the T2/flair sequence. She also developed worsening headaches for which we prescribed dexamethasone at eight milligrams a day in divided doses.

After receiving two cycles of erlotinib and bevacizumab therapy (2 week cycle), her headache symptoms resolved, and she was able to resume taking care of her child with cerebral palsy without assistance. We then gradually stopped the dexamethasone. Repeat imaging studies after 3 months of treatment demonstrated that the left hilar mass and pulmonary metastases were decreasing, and the brain metastases were decreasing in size and had less enhancement (Figs. 1b, 2b, d, and e). Based on patient-initiated consultation at an outside institution, she requested a change to pemetrexed and bevacizumab on a 3-week schedule. She was on this therapy regimen of ten cycles for 7 months (Figs. 1 and 2), the results being a continued slow response in her lung as well as stability of her brain lesions. She eventually developed renal insufficiency, and her therapy was changed back to erlotinib and bevacizumab. For the past 13 months, her disease has remained stable and she remains active. She is tolerating erlotinib and bevacizumab well and has currently been on continuous bevacizumab therapy for greater than 2 years.

Discussion

NSCLC with brain metastases have poor outcomes with limited therapeutic options after WBRT [8]. Bevacizumab for advanced non-squamous NSCLC is FDA approved in combination with chemotherapy, and response in the brain should demonstrate similar efficacy as in extracranial systemic disease. Metastatic brains lesions enhance with contrast revealing disruption of the blood–brain barrier [9, 10]. The concern for hemorrhage with bevacizumab has lessened based on increasing clinical experience, which includes greater than 500,000 patients treated, evaluation of completed clinical trials, and the AVF3752g safety clinical trial [5, 6]. This has led to guideline changes in NCCN and inclusion of patients in current clinical trials, however, patients need to have treated and clinically stable brain metastases [7, 11].

Our patient had disease progression in the chest and brain when bevacizumab was added, initially combined with erlotinib. Although progression of brain lesions is an exclusion criteria for the AVF3752g trial, our goal was to provide symptomatic relief based on the experience of bevacizumab for GBM [4]. Vascular endothelial growth factor (VEGF) was named permeability factor [12], and as the target of bevacizumab treatment results in less permeability with a decrease in peri-tumoral edema [13]. This frequently results in an early clinical benefit and has a steroid sparing effect [4]. On brain MRI images less enhancement of the tumor can be seen, along with decreased edema on T2/flair sequences. With the caveats of a case report, our case with a favorable clinical outcome combined with the low risk of hemorrhage with bevacizumab leads us to recommend consideration of

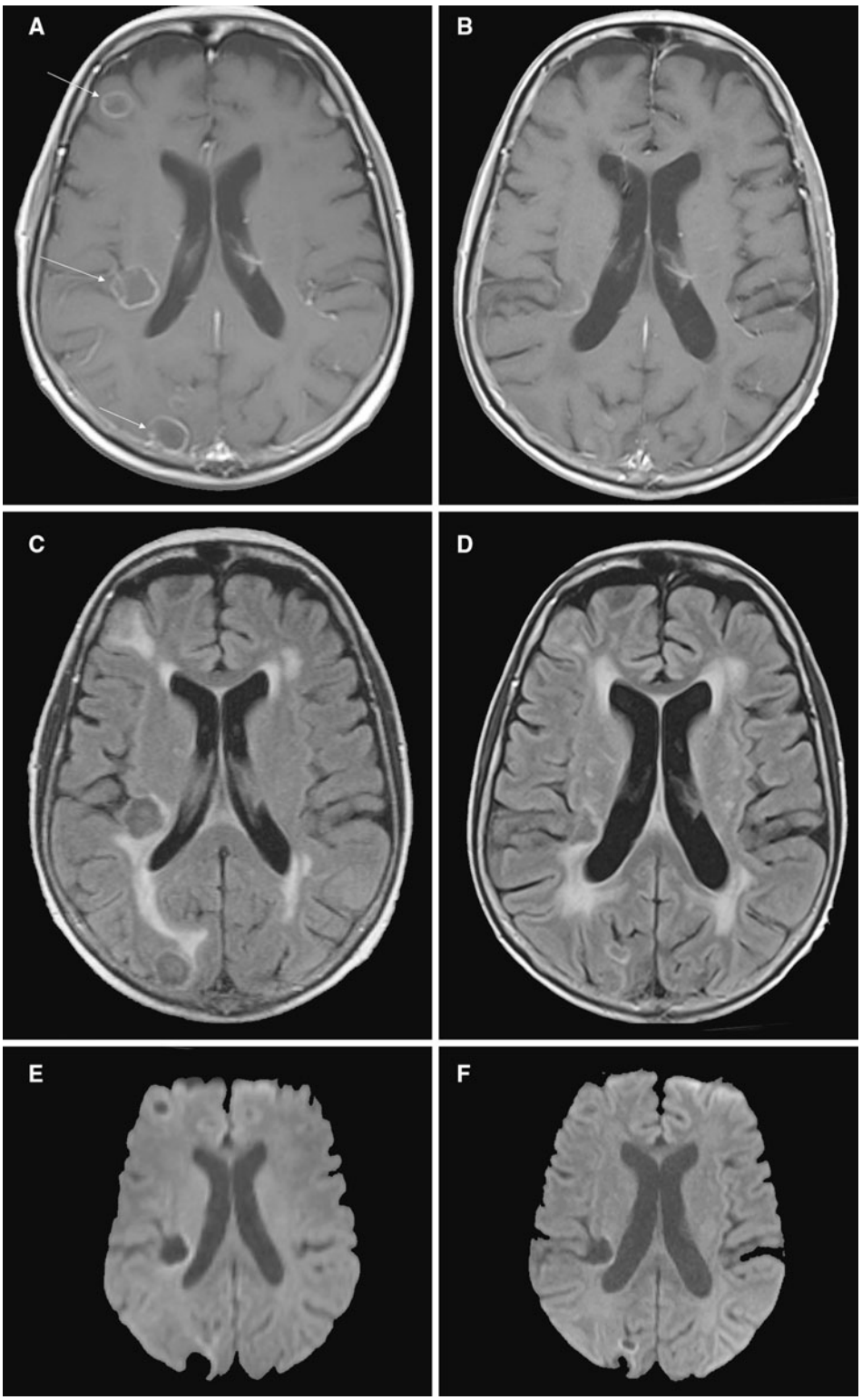

Fig. 2 **a**, **c**, and **e** are MR images of the brain prior to treatment with bevacizumab: **a** T1W post-Gadolinium (Gd) contrast, **c** T2W Flair, and **e** DWI b1000. **b**, **d**, and **f** are MR images of the brain after treatment with bevacizumab: **b** T1W post-Gd contrast, **d** T2W Flair, and **f** DWI b1000. On image **a** the Gd post-contrast T1W, three prominent ring-enhancing lesions (*arrows*) are seen in the right cerebral hemisphere with a large amount of vasogenic edema, which is better seen on image **c**, the T2W Flair image. On the corresponding images, **b** & **d**, complete resolution of two of the masses and marked decrease in the third mass. In addition, the amount of enhancement has decreased as has the vasogenic edema. On the pre-bevacizumab DWI image **d**, minimal high signal in the tumor walls is seen. On the post-bevacizumab DWI image **f**, similar high signal is present in residual enhancing portion of the tumor wall, demonstrating residual injury

treatment of symptomatic brain metastases without the restriction of having disease control.

She received the same benefit from bevacizumab in the brain as her systemic disease, and her clinical course has been remarkable, especially as she progressed on first-line systemic treatment. Her prognosis based on Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis (RPA) or graded prognostic assessment (GPA) for patients with brain metastases would be a median survival of 3–4 months, versus greater than 2 years that she has shown [8, 14]. This likely reflects her having a responsive EGFR-mutant allele NSCLC and receiving aggressive treatment, and that prognosis for treatment sensitive cancers in the brain is likely to be greater than RPA and GPA prognostication, which as yet does not factor tumor histology or biology.

Conflict of interest None.

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