Annals of Clinical Case Reports

Case Report
Published: 07 Feb, 2019

Long term Control of Metastatic Adenocarcinoma of the Lung to the Brain with Radiotherapy, Systemic Chemotherapy and Bevacizumab

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Abstract

The Central Nervous System (CNS) is one of the common sites of metastasis for advanced lung cancer. CNS metastases often cause significant morbidity and survival after diagnosis is dismal. Though stereotactic radio surgery has improved the outlook for some of these patients, there remains a need to develop additional therapies to control brain disease, especially with recent advancements in control of extra-CNS tumor. Systemic chemotherapy with Bevacizumab, an angiogenesis inhibitor, has shown promising activity in metastatic non-small cell lung cancer. Studies have shown that initial concern for excessive risk of CNS bleeding was unfounded and bevacizumab is now approved as second line treatment for glioblastoma. Here we present a case of metastatic lung cancer to the brain treated with multiple local and systemic therapies including Bevacizumab with over 4 years of control of his CNS disease. We also review the evidence regarding the safety and efficacy of Bevacizumab in this setting.

Keywords: Bevacizumab; CNS metastasis; NSCLC; Vascular endothelial growth factor

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Received Date: *08 Jan 2019*
Accepted Date: *04 Feb 2019*
Published Date: *07 Feb 2019*

Citation:
Tefera K, Breneman J, Woeste KM, Kamireddy C, Latif T. Long term Control of Metastatic Adenocarcinoma of the Lung to the Brain with Radiotherapy, Systemic Chemotherapy and Bevacizumab. Ann Clin Case Rep. 2019; 4: 1593.

ISSN: 2474-1655

Introduction

Central nervous system metastases are one of the most common complications of cancer. The exact incidence of this complication is unknown but population-based studies have estimated the incidence of clinically detectable metastatic brain tumors as between 7 and 14 persons per 100,000 populations [1]. Based on these calculations Fox et al. [1] estimated that over 43,000 patients were diagnosed with brain metastases in the United States in 2010, and autopsy studies suggest that the actual incidence may have exceeded 250,000 when patients with sub-clinical disease are included. This represents a significant burden of disease that is expected to rise as better therapies to control systemic disease result in improved overall survival.

Lung cancer is the leading cause of cancer deaths in the U.S [2] and Central Nervous System (CNS) metastasis is common in advanced lung cancer [3]. Approximately 20% to 25% of patients with advanced Non-Small Cell Lung Cancer (NSCLC) have brain metastases at diagnosis. A recent study showed a median survival of 10 months with use of radio surgery [4]. Current therapeutic options available for CNS metastasis include whole brain radiation, surgical resection, radio surgery and stereotactic radiation depending upon the number, location and size of brain metastases. However, in spite of the increasing number of therapeutic options for brain metastases, long term survivors are rare, with five year Overall Survival (OS) for stage IV disease less than five percent, the number is even less with patient with brain metastasis [5].

Systemic chemotherapy traditionally has a limited role in the treatment of brain metastasis. The Blood Brain Barrier (BBB) is widely considered to limit chemotherapy penetration into CNS though the mechanism for this is not clear and some studies have questioned the role of BBB in this setting. Most chemotherapy agents have limited brain penetration due to their large molecular size, and agents with good brain penetration such as temozolomide have poor activity against primary lung cancer [6]. In this report, we present a patient with adenocarcinoma of the lung and multiple CNS metastases who enjoyed an extended interval free of CNS recurrence while treated with systemic chemotherapy and bevacizumab.

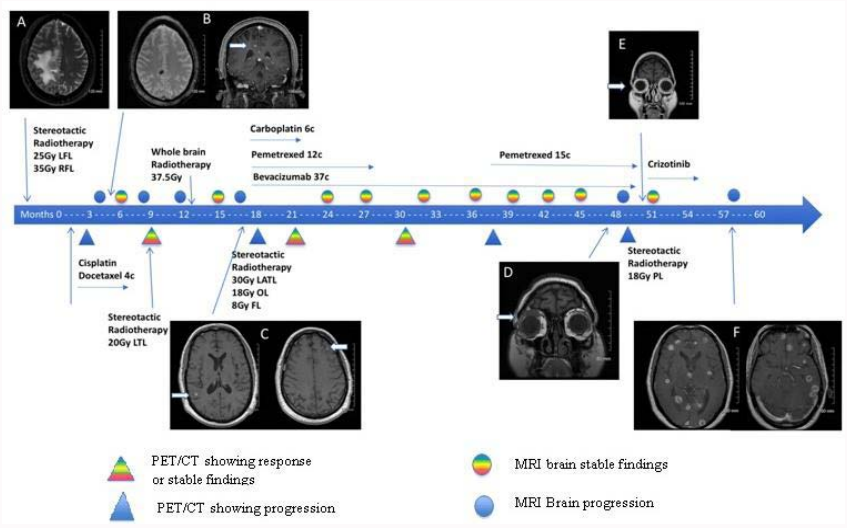

Figure 1: A. MRI of the brain at presentation showing large mass with significant vasogeneic edema. **B.** MRI of the brain five month after the initial diagnosis showing new metastatic lesions (arrows). **C.** MRI of the had Prior to the start of Bevacizumab treatment (at 16 months after the initial diagnosis) showing new metastasis (arrows). **D.** MRI of brain showing orbital metastasis at 48 months from diagnosis (arrow). **E.** MRI brain showing improvement in orbital metastasis after radiotherapy (arrow). **F.** MRI of brain at about 58 months since diagnosis showing significant progression in brain metastasis.
LFL: Left Frontal Lobe; RFL: Right Frontal Lobe; LTL: Left Temporal Lobe; LATL: Left Anterior Temporal Lobe; OL: Occipital Lobe; FL: Frontal Lobe; PL: Parietal Lobe

Case Presentation

A 47-year-old African American non-smoker male with no past medical history presented with right side weakness and headache. Brain Magnetic Resonance Imaging (MRI) showed a homogeneously enhancing intra-axial lesion within the posterior right frontal lobe near the falx with extensive vasogenic edema (Figure 1) and effacement of the overlying cortical sulci and a second 2 mm enhancing lesion centered within the cortex of the left frontal lobe was also noted. CT scan of chest showed a 3.7 cm × 2.5 cm lung lesion and an incidental finding of Pulmonary Embolism (PE). No other sites of disease were present on FDG PET/CT. He was started on anticoagulation, and biopsy of the lung lesion showed poorly differentiated adenocarcinoma of lung. Fluorescent in situ hybridization for EGFR and KRAS was negative and the specimen was insufficient for ALK analysis. His brain metastases were treated with stereotactic radiation therapy, 20 gray in one fraction to the left frontal lobe lesion and 35 Gray in five fractions to the right frontal lobe lesion. He then began chemotherapy with Cisplatin and Docetaxel for treatment of his primary tumor.

MRI of the brain 3 months following radio surgery showed decreased size of the treated lesions but a new 2 mm left posterior temporal lesion, which was treated with 20 Gy in 1 fraction. PET/CT scan after 4 cycles of chemotherapy showed decreased size of his lung primary. A brain MRI done 5 month after diagnosis showed a response of his treated metastases with no new lesions (Figure 1). However, a brain MRI done 4 months later showed multiple (>6) new lesions, and he was treated with 37.5 gray of whole brain radiation in 15 fractions, followed by a radiosurgery boost to 3 lesions that persisted on follow-up imaging.

A subsequent brain MRI done 4 months later (17 months after diagnosis) showed 10 new enhancing lesions, all of which were treated with radio surgery. PET/CT at that time showed increased disease burden in the chest as well as new metastatic foci in the left anterior chest wall, left shoulder, acetabuli, and left adrenal gland.

He was started on carboplatin, pemetrexed and Bevacizumab with good tolerance. After completion of four cycles of chemotherapy (22 months from diagnosis) CT/PET showed resolution of increased FDG uptake in the mediastinum, left chest wall, left axilla, left adrenal gland, bilateral acetabula, and decreased activity in the lung. He received two more cycles of combination chemotherapy and then was placed on maintenance therapy with Bevacizumab and pemetrexed. Pemetrexed was discontinued due to insurance issues after 6 additional cycles and he continued Bevacizumab 7.5 mg/kg every three weeks for 10 additional cycles.

Pemetrexed was added again (six month after it was dropped for insurance issue and 36 month after the original diagnosis) due to progression of systemic disease. He received 15 additional cycles of Pemetrexed along with Bevacizumab with good control of disease until further progression in lung disease and he underwent stereotactic radio surgery to his primary lung tumor. His systemic therapy was held in anticipation of his lung radio surgery to lung lesion. Brain MRI before chest radiotherapy continued to show stable disease however another brain MRI at about 48 months after initial presentation showed new enhancing lesion in high right parietal lobe and abnormal asymmetric enhancement within the superior right orbit, which encases the superior and lateral rectus muscles. Throughout the time between the MRI brain at about 16 months after initial presentation and 48 months after presentation he was maintained on Bevacizumab treatment for the most part and none of the eight MRI brains obtained during this time period show any progression in CNS disease. He maintained excellent functional life with full time work and family life (Figure 1).

He had another 18 Gray stereotactic radiotherapy to parietal lobe lesion and another follow up MRI showed worsening findings in the orbit and he received radiotherapy to orbit too. He had clinical decline with worsening chest findings including new pleural effusion, Genomic analysis showed ROS1 mutation and he was started on Crizotinib with clinical response and symptom control for several weeks, unfortunately he had further progression with new adrenal

metastasis and progressive brain disease on repeat MRI 4 months later. He decided to enroll on hospice care and died after about 60 months of original diagnosis.

Discussion

Patients who fail initial local therapy or are not candidates for local therapy (resection, stereotactic radiosurgery or whole brain radiation treatment) for their CNS metastasis of adenocarcinoma of lung have a very poor prognosis due to limited number of salvage treatment options. Finding an effective modality to treat or prevent brain metastases for these patients is an important challenge facing lung cancer researchers, especially with the emergence of better therapies to control systemic disease, resulting in improved overall survival.

Our patient experienced multiple episodes of CNS metastasis, which occurred even when systemic disease was under control. However, long-term control of his brain disease was observed coincidental with the start of Bevacizumab, pemetrexed and carboplatin given to treat his progressive systemic disease. It is possible that the combination of carboplatin and pemetrexed controlled not only the systemic relapse but also further progression of CNS disease. Some recent studies using platinum and Pemetrexed suggested that systemic chemotherapy could result in objective response to brain metastasis from lung cancer and radiotherapy can be delayed in some patients with asymptomatic brain metastasis [7,8]. However, we believe Bevacizumab may have played a prominent role in the prevention of new CNS metastases as this was the only drug our patient consistently received during his prolonged CNS disease-free interval, and his CNS disease relapsed soon after discontinuation of Bevacizumab and pemetrexed at the time of his systemic progression.

Bevacizumab is a humanized monoclonal antibody that binds to Vascular Endothelial Growth Factor (VEGF) receptor and inhibits angiogenesis. Angiogenesis plays significant role in growth and metastasis of cancer cells [9,10]. Studies have shown that when metastatic tumors grow beyond a few millimeters, angiogenesis is triggered resulting in the formation of abnormal capillaries that lack tight junctions facilitating fenestrations. The blood brain barrier is disrupted, allowing variable passage of water-soluble agents [10,11]. VEGF also increase vascular permeability of the blood-brain barrier and produces vasogenicedema. Bevacizumab binds VEGF and prevents the interaction of VEGF with target receptors on the surface of endothelial cells causing reduced tumor angiogenesis and inhibits tumor growth. Binding to the endothelial cell surface receptors helps to bypass the Blood Brain Barrier (BBB) and have effect on the CNS [12,13].

FDA approves Bevacizumab in combination with chemotherapy for treatment of metastatic lung cancer however its effectiveness in controlling brain metastasis is largely unknown [14].

The first phase 1 clinical trial evaluating Bevacizumab for metastatic cancer had one fatal cerebral hemorrhage in a patient with hepatocellular carcinoma [15], and due to this event, patients with CNS metastasis were excluded in subsequent clinical trials. However, more recent trials have shown no excess risk of Bevacizumab in patients with brain metastases. The PASSPORT (AVF3752 g) trial treated patients with brain metastases Bevacizumab (15 mg/kg) every 3 weeks with platinum-based doublet therapy or erlotinib, continuing until disease progression or death. In 106 evaluable patients, no episodes of grade ≥ 2 CNS hemorrhage were noted [16]. De Braganca et al. [17] reported safe administration of Bevacizamab in six patients with active CNS metastases, applying RECIST criteria 2 patients achieved partial response, three patient had stable disease one patient had progression. Median progression-free survival was 7.8 months and median overall survival was 14.1 months following initiation of bevacizumab [17]. Five prospective studies- PASSPORT, ATLAS, BeTa, ERACLE and PRONOUNCE trials showed a low rate of CNS hemorrhage in patients with Brain metastasis treated with Bevacizumab [16,18-21]. A retrospective analysis of the AVAIL trial [22], showed lower rate of brain metastasis as first site of recurrence in the patients who received bevacizumab compared to the control group receiving standard chemotherapy (2.6% *vs.* 5.8%; P=0.01), also with a lower risk of brain metastasis development over time (HR=0.36, P=0.001). Furthermore, the median time to development of brain metastasis was shorter in the control group 4.5 *vs.* 7.8 months with bevacizumab, P<0.01 [23].

In our patient, new CNS disease appeared despite the systemic disease being controlled and he also had relapse of his systemic disease despite his CNS disease being controlled. Although there could be other possible explanation for this phenomenon, we believe that the combination of these clinical findings argues metastatic diseases can behave independently. As for systemic relapse, there is a good evidence for continuing maintenance treatment in adenocarcinoma to prevent a recurrence of systemic disease. There are almost no studies exist to guide any systemic treatment for CNS metastatic lung disease. There is dire need to design more prospective studies to test the efficacy of Bevacizumab in this setting.

Conclusion

Although there is enough evidence from several case reports and retrospective analysis that Bevacizumab is safe to administer in patients with active or treated brain metastasis its efficacy in this setting is not well established. Our case demonstrates a prolonged period of freedom from new brain metastases coinciding with the administration of systemic chemotherapy and Bevacizumab. The case also showed that of Bevacizumab may have role in preventing development or progression of CNS metastasis. Bevacizumab should be evaluated for prevention and treatment of CNS metastasis for advance lung cancer.

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