Bevacizumab for Critical Brain Metastases in a Patient with Pulmonary Pleomorphic Carcinoma

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Abstract

Bevacizumab was initially contraindicated in patients with brain metastases, but several reports have shown the efficacy and safety of bevacizumab for brain metastases. We herein report the case of a patient with pulmonary pleomorphic carcinoma for which bevacizumab plus weekly paclitaxel following whole-brain radiotherapy (WBRT) was effectively and safely administered for critical and refractory brain metastases. Although the 50-year-old male patient received WBRT with anti-edema therapies for progressive brain metastases, his clinical symptoms deteriorated rapidly. After the completion of WBRT, we administered bevacizumab plus weekly paclitaxel, and his neurological symptoms improved dramatically. Brain magnetic resonance imaging demonstrated a marked response by the brain metastases and improved brain edema. This case suggested both synergism between WBRT and bevacizumab, and an anti-edema effect of bevacizumab. Bevacizumab may be therefore a potent therapeutic option for patients with refractory brain metastases.

Key words: bevacizumab, brain metastases, brain edema, brain hemorrhage, pleomorphic carcinoma


Introduction

Brain metastases occur in approximately 25 to 30% of patients with non-small cell lung cancer (NSCLC) (1, 2). Because patients with advanced NSCLC are living longer, the incidence of brain metastases is increasing. Treatment with whole-brain radiation therapy (WBRT) and steroids is the standard care regimen for patients with multiple brain metastases. Stereotactic radiosurgery or neurosurgical resection is performed for solitary or oligometastatic disease. Conventional systemic chemotherapies appear to be ineffective, likely because they might not sufficiently cross the blood-brain barrier (1, 3). Generally, the prognosis for patients with brain metastases remains poor, and more effective therapies should be developed.

Bevacizumab is a recombinant humanized monoclonal antibody directed against vascular endothelial growth factor (VEGF), an essential endothelial cell mitogen and survival factor, and a key factor in tumor-associated angiogenesis. The addition of bevacizumab to carboplatin plus paclitaxel for the treatment of NSCLC was shown to significantly improve overall survival (4). Bevacizumab combined with carboplatin plus paclitaxel is a standard first-line treatment for metastatic NSCLC. In early-phase clinical trials, bevacizumab was contraindicated in patients with brain metastases, based on a report of fatal brain hemorrhaging in a patient with brain metastatic hepatocellular carcinoma (5).

However, several reports have demonstrated the safety of bevacizumab for brain metastases (6-11). With regard to previously treated inactive brain metastases after WBRT, stereotactic radiosurgery, and/or neurosurgery, the safety of bevacizumab was shown in a prospective cohort study (6). There were no grade ≥2 cerebral hemorrhages among 106 patients with brain metastases who received bevacizumab in the PASSPORT study (6). Another study that included patients with active brain metastases also confirmed that the risk of cerebral hemorrhage of incidental or quiescent metastases did not significantly increase when bevacizumab was administered (7).

Although evidence of the safety of bevacizumab is accumulating, little is known about the efficacy of bevacizumab
for brain metastases. We herein describe a case of pulmonary pleomorphic carcinoma in which bevacizumab plus weekly paclitaxel was effectively and safely administered for critical and refractory brain metastases.

Case Report

A 50-year-old man was diagnosed with locally advanced pulmonary pleomorphic carcinoma (PPC) of the left upper lung. He underwent neoadjuvant chemoradiation therapy with cisplatin plus pemetrexed. Surgery was performed but the tumor was unresectable due to strong invasion into the descending aorta and left pulmonary artery (Fig. 1). After surgery, the patient complained of gait disturbance, and brain magnetic resonance imaging (MRI) revealed multiple brain metastases. He sought further treatment at our institute. After admission, we initiated WBRT (30 Gy/10 fractions) with anti-edema therapy using dexamethasone and glycerol. During WBRT, his consciousness deteriorated, and brain magnetic resonance imaging (MRI) revealed progressive tumors and severe brain edema (Fig. 2). Intratumoral hemorrhages were revealed on T1-weighted images, and the WBRT was considered to be ineffective.

After the completion of WBRT, the patient’s Glasgow Coma Scale score was 4 and his systolic blood pressure (BP) was 200 mmHg and higher, thus indicating Cushing phenomenon. His family requested further active therapies for his life-threatening condition. We proposed bevacizumab therapy as a potentially effective agent, and provided a detailed explanation of the possible fatal adverse events, including brain hemorrhage deterioration. Despite the high-risk situation, the family agreed to bevacizumab chemotherapy. We administered bevacizumab (15 mg/kg, day 1) plus paclitaxel (70 mg/m2; days 1, 8, 15) every 3 weeks. After the initiation of this therapy, the patient’s consciousness improved dramatically and his BP gradually decreased. Brain MRI performed after two cycles of therapy demonstrated a marked response by the brain metastases (Fig. 3). A more moderate response was observed in the thoracic lesions (Fig. 4). This chemo-regimen was continued for six cycles. Six months after the initiation of bevacizumab, the patient contracted bacterial pneumonia, and he has only received supportive care.

Discussion

In this patient with PPC, bevacizumab plus weekly paclitaxel was effectively and safely administered to treat critical and refractory brain metastases. As noted above, several studies have demonstrated the efficacy and safety of bevaci-
bevacizumab for brain metastases from lung cancer (6-11), and other types of cancers (12-14), especially in recurrent glioblastoma patients. In patients with chemotherapy- and radiotherapy-refractory glioblastoma, bevacizumab showed effectiveness as a monotherapy or in combination with cytotoxic agents (15-17). Therefore, bevacizumab may be a promising treatment option for refractory brain metastases of many cancers.

In our patient, bevacizumab was initiated 1 week after the completion of WBRT. The safety of bevacizumab was confirmed in other patients with previously treated, inactive brain metastases (6). In the present case, although we cannot estimate how WBRT may have contributed to its safety, bevacizumab was safely administered even though the patient had a pre-existing intratumoral hemorrhage. The tumor response to bevacizumab may have reduced vascular permeability, resulting in discontinuation of the hemorrhage.

Most of our patient’s brain tumors exhibited marked responses to bevacizumab, except for the brainstem tumor, which contained an intratumoral hemorrhage. Although the tumor reduction was relatively small (from Fig. 2b to Fig. 3b), the surrounding edema improved (from Fig. 2d to Fig. 3d). This suggests an anti-brain edema effect of bevacizumab. Several reports have demonstrated bevacizumab’s effectiveness against radiation necrosis induced by capillary permeability caused by cytokines, such as VEGF (18-21). Another study demonstrated that bevacizumab had corticosteroid-sparing effects in high-grade glioma (22). These reports support a potent anti-edema effect of bevacizumab, and suggest that it may be an effective treatment option for refractory brain edema.

PPC is rare, accounting for 0.1-0.4% of all lung cancers, and it has a poor clinical prognosis (23). The World Health Organization classification defines PPC as a poorly differentiated type of NSCLC, with at least 10% spindle cells and/or giant cell components. In general, PPC is characterized by a poor response to conventional chemotherapies and disappointing clinical outcomes (24, 25). Some reports described epidermal growth factor receptor (EGFR) gene mutations (approx. 20%) in PPC (26). However, in our patient, both EGFR-sensitive mutations and anaplastic lymphoma kinase (ALK) fusions were negative, and molecular-targeted therapies for the driver oncogenes were not available. Notably, some studies have demonstrated VEGF to be highly expressed in many cases of PPC (26, 27). According to the above reports, VEGF-targeted therapies such as bevacizumab may be potent treatment options in patients with advanced PPC. In our patient, bevacizumab treatment produced a

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Figure 2. Gadolinium-enhanced T1-weighted images (a, b) show progressive tumors. Fluid-attenuated inversion recovery (FLAIR) images (c, d) reveal severe brain edema due to tumors.
mixed response: it was highly effective in the brain metastases, but a more moderate effect was observed in the thoracic lesions.

We selected weekly paclitaxel as the combination agent with bevacizumab, although there was admittedly little evidence to promote it. A preclinical investigation found that paclitaxel has stronger synergy with bevacizumab than other agents (28). Among the several regimens used in combination with bevacizumab for non-squamous NSCLC, a definitive survival benefit was only demonstrated in carboplatin plus paclitaxel with bevacizumab (4). A current retrospective report also suggested the efficacy and safety of weekly paclitaxel plus bevacizumab for chemorefractory patients with non-squamous NSCLC (29). Based on the safety data in this report, we considered weekly paclitaxel safe to administer with bevacizumab in a patient such as ours, with a poor general condition. Weekly paclitaxel may minimize adverse events and maximize efficacy when used in combination with bevacizumab, and this can be a potentially effective treatment option for chemorefractory patients with a poor general condition.

In the ARIES (Avastin Regimens: Investigation of Treatment Effects and Safety) trial, the safety of up-front bevacizumab combination regimens was prospectively investigated in patients with non-squamous NSCLC. In 182 (9.3%) of the 1,967 patients with poor Eastern Cooperative Oncology Group performance status (PS) [PS2, 161 (8.2%) and PS3-4, 21 (1.1%)], the prevalence of bevacizumab-related adverse events, such as pulmonary hemorrhage, did not significantly increase (30). Bevacizumab combination regimens may be effective and safe even in patients with poor PS, and these regimens warrant further studies.

The possible synergistic effect of bevacizumab and WBRT should thus be considered. Bevacizumab has shown direct antivascular effects with enhanced radiosensitivity in both preclinical and clinical settings (31). VEGF-targeted agents as potential radiosensitizers have been investigated for glioblastoma (32, 33). The efficacy and safety of bevacizumab with chemotherapy and radiotherapy have been assessed in clinical studies for the treatment of newly diagnosed glioblastoma (34, 35). However, in the present patient, at one week after the completion of WBRT, bevacizumab plus paclitaxel was administered and his clinical symptoms improved rapidly. Although the possibility of a delayed effect of WBRT cannot be excluded, the patient’s clinical symptoms improved immediately after the bevacizumab was initiated. We therefore speculate that the dramatic response was due to bevacizumab rather than WBRT, or to a syner-
gistic effect between the two.

In conclusion, a dramatic response to bevacizumab plus paclitaxel salvaged a patient with PPC who suffered from critical and refractory brain metastases. Our findings suggest that bevacizumab can be a therapeutic option for patients with refractory brain metastases; however, further research is needed to confirm the efficacy and safety of bevacizumab for active brain metastases.

The authors state that they have no Conflict of Interest (COI).

References


