# Bevacizumab as Front-line Treatment of Brain Metastases from Solid Tumors: A Case Series

FABLE ZUSTOVICH, ALESSANDRA FERRO, GIUSEPPE LOMBARDI, VITTORINA ZAGONEL, PASQUALE FIDUCCIA and PATRIZIA FARINA

*Instituto Oncologico – IRCCS, Padua, Italy*

**Abstract.** *Background: Despite the large use of bevabizumab in the treatment of primary tumors of the brain, there is only limited experience with brain metastases (BM) and no experience in the treatment of previously untreated secondary brain lesions. Patients and Methods: We treated patients with BM, not suitable for local treatment, with a bevacizumab-based therapy associated with chemotherapy or interferon-α, as indicated for the primary cancer type. Results: We studied 18 patients with BM mostly from lung and renal adenocarcinoma, and the majority of patients had a treatment-naïve brain disease. Bevacizumab was found to be effective: the response rate was 60% partial responses with 40% disease stabilizations. The progression-free survival was 14 months and the overall survival was 15 months. Moreover, bevacizumab has a high capability of providing a long-lasting clinical benefit and reducing edema. Conclusion: Bevacizumab for treatment of BM is feasible and the efficacy data are very encouraging.*

The use of bevacizumab in combination with other anticancer drugs has resulted in a significant improvement of efficacy outcome in several diseases leading to its Food and Drug Administration (FDA) and European Agency for the Evaluation of Medicinal Products (EMEA) approval for diseases such as lung, kidney, colorectal and breast cancer and high grade malignant gliomas. Bevacizumab is a recombinant humanized monoclonal antibody that binds to human Vascular endothelial growth factor (VEGF), preventing its interaction with the receptors on the surface of endothelial cells. VEGF is one of the most important pro-angiogenic factors involved in tumor growth: it stimulates the formation of new blood vessels, acts as a survival factor and increases vascular permeability, which might facilitate tumor dissemination *via* the circulation. Bevacizumab obstructs the VEGF pathway and has been shown to reduce tumor perfusion, vascular volume, microvascular density, interstitial fluid pressure and the number of circulating mature and progenitor endothelial cells in patients with carcinomas (1). Moreover, bevacizumab has been suggested to be able to influence the tumor blood vessels, resulting in a more efficient delivery and action of chemotherapies (2).

Brain metastatic disease is a frequent complication in patients with cancer, especially those with lung, breast and kidney cancer (3). Such patients usually have a poor quality of life and a dismal prognosis with a median expected overall survival of approximately 4-7 months if a local treatment, such as neurosurgery or radiosurgery, is not indicated (4). Brain metastatic lesions are quite often accompanied by possibly considerable perilesional edema, which is frequently the first contributor to neurological symptoms. Corticosteroids are used to contain or to alleviate brain edema and are able to reduce the mass effect, but they are associated with several debilitating long-term side-effects. Nowadays, there is evidence that bevacizumab is able to induce a significant anti-edemigenous effect by transiently normalizing the tumor vasculature and by restoring the integrity of the blood-brain barrier (5). At first, patients with brain metastatic disease were excluded from bevacizumab-based clinical trials because of the suspicion a high risk of brain hemorrhage (6), but a retrospective study on patients with brain metastases from lung adenocarcinoma has demonstrated no increase in brain hemorrhage for treated central nervous system (CNS) lesions (7).

On the basis of these observations, we started treating symptomatic metastatic brain disease not suitable for other specific therapy with a bevacizumab-based therapy.

## Patients and Methods

Patients with brain metastatic diseases not suitable for specific local treatment (neurosurgery or radiotherapy) were treated with a bevacizumab-based therapy depending on the primary tumor. Patients with lung adenocarcinoma received bevacizumab at 7.5

*Correspondence to:* Fable Zustovich, MD, Istituto Oncologico Veneto – IRCCS, via Gattamelata 64, 35127 Padova, Italy. Tel +39 0498215914, Fax +39 0498215904, e-mail: fable.zustovich@ioveneto.it

*Key Words:* Brain, metastasis, bevacizumab, lung, kidney, cancer, chemotherapy, interferon-α.

Table I. *Patients' characteristics*.

| Characteristic (n=18) | Number of patients |
|---|---|
| Gender | |
| Male | 13 |
| Female | 5 |
| Age (years) | |
| Median | 64.6 |
| Range | 41-75.9 |
| Primary tumor site | |
| Lung | 13 |
| Kidney | 4 |
| Endometrial carcinoma | 1 |
| ECOG PS | |
| 0 | 6 |
| 1 | 10 |
| 2 | 2 |
| 3 | 0 |
| Other sites of metastasis | |
| Lung | 8 |
| Bone | 4 |
| Liver | 3 |
| Lymph nodes | 8 |
| Adrenal gland | 2 |
| Prior therapy of CNS metastases | |
| Surgery1 | |
| WBRT/SRS | 2 |

WBRT: Whole-brain radiotherapy; SRS: stereotactic surgery; CNS: central nervous system; ECOG PS: eastern cooperative oncology group performance status.

or 15 mg/kg on day 1 associated with cisplatin at 75 mg/m$^2$ on day 1 and gemcitabine at 1,250 mg/m$^2$ on days 1 and 8 every 21 days for six cycles, with bevacizumab being continued as maintenance therapy. Patients with kidney cancer received bevacizumab at 10 mg/kg plus interferon-α 3 million of international units (MIU)*3/week every two weeks until disease progression. The patient with endometrial adenocarcinoma received bevacizumab at 15 mg/kg on day 1, cisplatin at 50 mg/m$^2$ on day 1 and gemcitabine at 1,000 mg/m$^2$ on days 1 and 8 every three weeks.

Toxicity was assessed the day before every treatment administration using the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) (8) and disease evaluation was performed every three cycles of chemotherapy for patients with lung and endometrial adecarcinoma and every six administrations of bevacizumab for patients with renal cancer. CNS involvement has been monitored by gadolinium-enhanced magnetic resonance tomography (MRT) and extracerebral disease with contrast-enhanced computed tomography (CT) scan of the body. Responses were evaluated with Response Evaluation Criteria In Solid Tumors (RECIST) (9).

Due to the low numbers of cases, a non-statistical analysis was performed and the survival curves were obtained using the Kaplan Meier method. Analyses were performed using the GraphPad Prism statistical package (release 5; GraphPad Software Inc. San Diego, CA, USA).

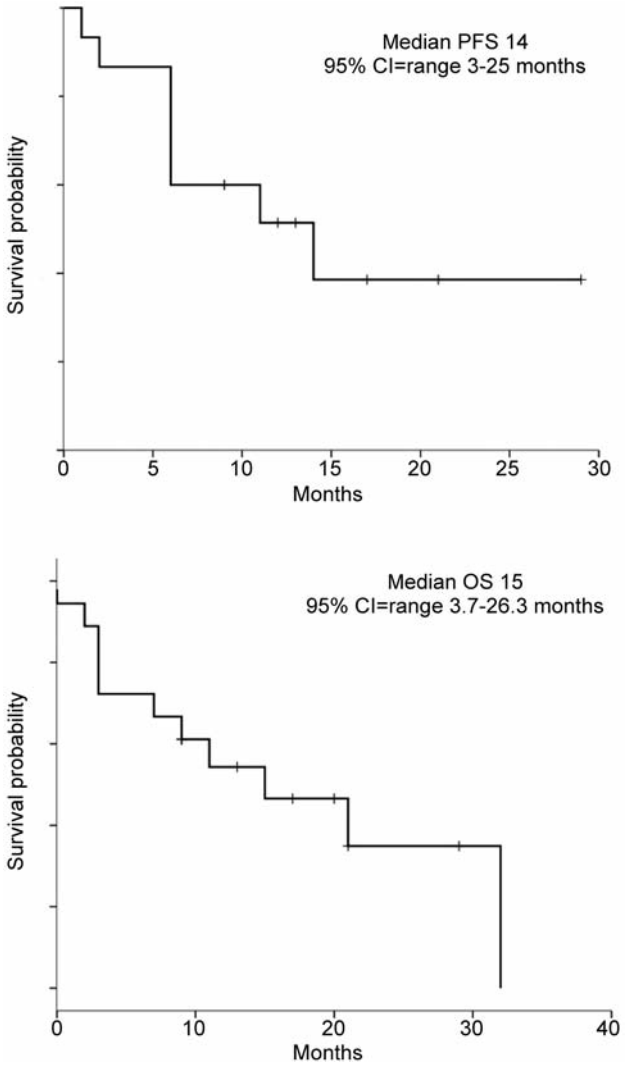


Figure 1. *Progression-free survival (PFS) and overall survival (OS) curves for the overall patient group (n=18).*

## Results

We included 18 patients, 13 were males and 5 were females. The median age at the beginning of the therapy was 64.6 (range=41.0-75.9) years. Thirteen patients had lung adenocarcinoma, four had renal adenocarcinoma and one had an endometrial carcinoma. (see Table I for other characteristics). At the time of analysis, all patients were evaluable for toxicity and 15 out of 18 were evaluable for response [ten with non-small cell lung carcinoma (NSCLC), four with renal adenocarcinoma and one with endometrial carcinoma]. The response rate was 60% (partial responses) with 40% of disease stabilizations, no case of progression was observed and one patient had a complete response. Three patients were not evaluable for response due to early

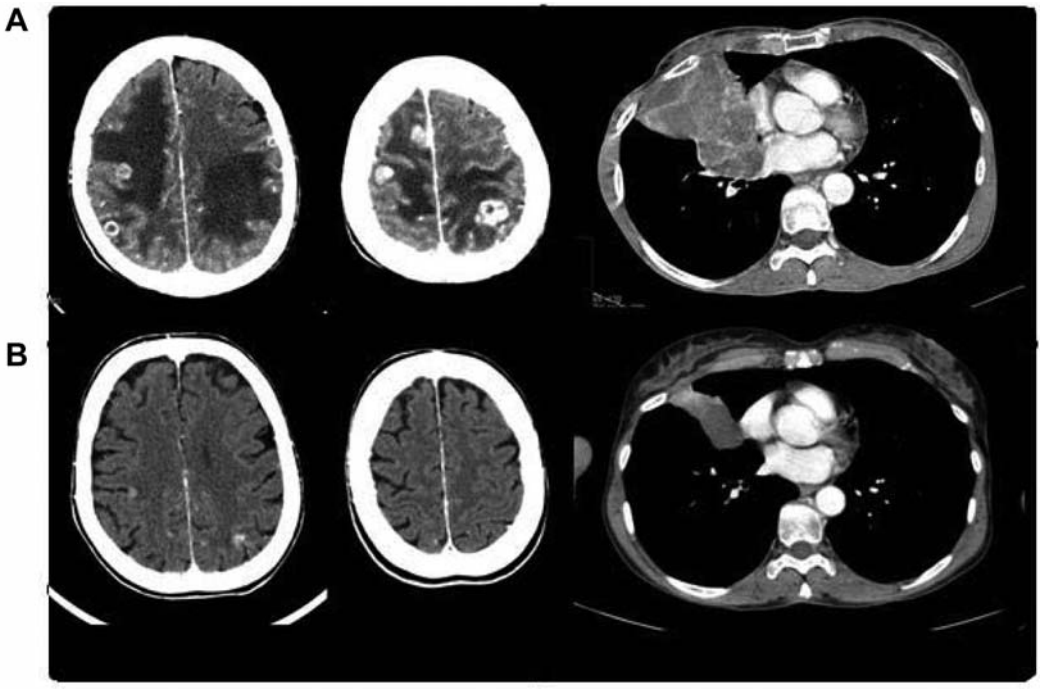


Figure 2. *Cerebral and thoracic computed tomography (CT) imaging of a patient with partial response. This patient is a 62-year-old woman with a non-small cell lung cancer with brain metastases. A: Brain metastases with perilesional edema and right pulmonary mass before treatment and B: after the treatment with bevacizumab-based chemotherapy.*

suspension of the therapy as a consequence of disease progression or life-threatening toxicity. The estimated progression-free survival (PFS) and overall survival (OS) based on the present data and for the overall patient group are promising: PFS was 14 [95% confidence interval (CI)=3.0-25.0] months and OS was 15 (95% CI=3.7-26.3) months (Figure 1). Figure 2 shows the CNS and extra-CNS response of a patient with lung adenocarcinoma.

With regard to toxicity, there were two cases of cerebral ischemia, a case of gastric perforation and a case of pulmonary embolism (Table II).

Table II. *Toxicity due to bevacizumab therapy by type and grade.*

| Type | Grade 1-2 | Grade 3-4 |
|---|---|---|
| Asthenia | 4 | 2 |
| Neutropenia | 1 | 2 |
| Nausea | 1 | - |
| Hypertension | 5 | - |
| Vascular venous (DVT+PE) | - | 1 |
| Thrombocytopenia | 2 | 1 |
| Anemia | 1 | - |
| Gastrointestinal disorders | - | 1 (Gastric perforation) |
| Proteinuria | - | - |
| Delayed healing | 1 | 1 |
| Hemorrhage | - | - |
| ATE | - | 2 (Stroke) |
| VTE | - | 1 (DVT) |

DVT: Deep venous thrombosis; PE: pulmonary embolisms; ATE: arterial thromboembolic event; VTE: venous thromboembolic event.

## Discussion

Our experience in treating patients with brain metastatic disease appears very promising, especially considering the fact that most of the patients did not have any specific treatment before receiving bevacizumab.

After prior experience using bevacizumab for the therapy of relapsed glioblastoma, we noticed a short survival time but a high clinical benefit, mostly reducing perilesional edema, sometimes with a long-lasting effect (10). Thus, after having seen good control of symptoms and long PFS and OS times in the initial patient group, we started treating most patients with brain metastases from solid tumors with a bevacizumab-based therapy, having official approval.

Results are sometimes surprising showing overall response rate of 60 % and no observed disease progression (control rate 100%); PFS was 14 months and OS was 15 months. The patient whose response is represented in Figure 2 had a PFS and an OS of 31.1+ months and is still receiving maintenance therapy with bevacizumab. In addition to these objective efficacy data, we have noticed, but not yet measured, a

Table III. *Previously published data and present series of patients' characteristics and results.*

| Author (ref) | Pt. | Gender/age/ primary tumor | Prior therapy for brain metastases | Treatment | CNS response | Extra-CNS response | PFS (months) | OS (months) |
|---|---|---|---|---|---|---|---|---|
| Bhaskara *et al*. 2008 (13) | 1 | Ma/62/Rectum | SRS | Bev+FOLFOX | PR | NR | 12 | NR |
| Labidi *et al*. 2009 (14) | 2 | Fe/64/Breast | None | Bev+Pacl | PR | NR | 6+ | NA |
| | 3 | Fe/44/Breast | WBRT | Bev+Pacl | PR | SD | 10+ | NA |
| Braganca *et al*. 2010 (15) | 4 | Ma/77/NSCLC | NSur, WBRT,TMZ | Bev | SD | SD | 10.9 | 14.6 |
| | 5 | Fe/59/NSCLC | NSur,WBRT, SRS,TMZ | Bev, and then Bev+CT | PR | PD | 10.3 | 14.1 |
| | 6 | Fe/60/NSCLC | SRS | Bev+PMX | SD | NE | 4.7 | 9.9 |
| | 7 | Ma/77/NSCLC | None | Bev+PMX | SD | SD | 2.4 | 9.8 |
| | 8 | Fe/74/NSCLC | PMX | Bev+PMX | PR | SD | 7.3 | 8.6 |
| | 9 | Fe/60/NSCLC | WBRT,PMX,ITCyt | Bev+ITCyt+Gem | SD | SD | 2.1 | 4.7 |
| Yen-Shen L *et al*. 2012 (16) | 10 | | | | | | | |
| | 11 | | | | | | | |
| | 12 | | | | | | | |
| | 13 | | | | | | | |
| | 14 | | | | PR n=9 | | | |
| | 15 | Fe/NR/breast | WBRT | Bev+Cis+Eto | SD n=2 | NR | 6.6 (median) | NR |
| | 16 | | | | PD n=1 | | | |
| | 17 | | | | | | | |
| | 18 | | | | | | | |
| | 19 | | | | | | | |
| | 20 | | | | | | | |
| | 21 | | | | | | | |
| Present series* | 22 | Fe/62/NSCLC | None | Bev+Cis+Gem | Near CR | PR | 31.1+ | 31.1+ |
| | 23 | Ma/41/NSCLC | None | Bev+Cis+Gem | SD | SD | 11.4 | 15.9 |
| | 24 | Ma/70/kidney | NSurg | Bev+Inf-alfa | CR | PD | 18.4+ | 18.4+ |
| | 25 | Fe/58/NSCLC | None | Bev+Cis+Gem | PR | PR | 0.9+ | 3.6 |
| | 26 | Ma/56/kidney | None | Bev+Inf-alfa | PR | PR | 20.3 | 33.2 |
| | 27 | Ma/73/kidney | SRS | Bev+Inf-alfa | PR | PR | 20.7+ | 20.7+ |
| | 28 | Ma/71/kidney | None | Bev+Inf-alfa | SD | SD | 6.5 | 12.3 |
| | 29 | Ma/69/NSCLC | None | Bev+Cis+Gem | SD | PD | 7.6+ | 8.2 |
| | 30 | Ma/65/NSCLC | None | Bev+Cis+Gem | SD | PD | 1.9 | 3 |
| | 31 | Ma/70/NSCLC | WBRT | Bev+Cis+Gem | SD | PD | 6.8 | 9.6 |
| | 32 | Ma/50/NSCLC | None | Bev+Cis+Gem | SD | PR | 7.2+ | 9.9 |
| | 33 | Ma/67/NSCLC | None | Bev+Cis+Gem | PR | PR | 14.6+ | 14.6+ |
| | 34 | Fe/75/NSCLC | None | Bev+Cis+Gem | PR | PR | 9.6+ | 9.6+ |
| | 35 | Ma/67/NSCLC | None | Bev+Cis+Gem | PR | PR | 8.2+ | 8.2+ |
| | 36 | Fe/67/endometrial carcinoma | None | Bev+Cis+Gem | PR | PR | 17.7+ | 17.7+ |

SRS: Stereotactic surgery; WBRT: whole-brain radiotherapy; NSurg: neurosurgery; TMZ: temozolomide; Pacl: paclitaxel; PMX: pemetrexed; ITCyt: intra-thecal cytarabine; Bev: bevacizumab; Cis: cisplatin; Gem: gemcitabine; Eto: etoposide; Inf-α: interferon-α; NSCLC: non-small cell lung cancer; SD: stable disease; PR: partial response; PD: progressive disease; NR: no response; NE: not evaluable; CR: complete response. *RR=15/18.

considerable gain in quality of life, allowing the reduction of high-dose dexamethasone administration. This early suspension of dexamethasone administration is possible solely due to the anti-edemagenous effect of bevacizumab. Soon after starting treatment, patients have a rapid relief of their neurological symptoms and dexamethasone administration may be reduced, even completely suspended.

Moreover, for patients treated with bevacizumab as front-line therapy for brain metastatic disease the administration of whole-brain radiation therapy may also be delayed, avoiding the associated detrimental effects on cognitive functions in case of long-term survival.

To our knowledge, no prior report considers the front-line therapy of brain metastases with bevacizumab. Other studies have reported a case series of patients treated with a bevacizumab-based therapy for brain metastatic disease (see Table III), but in all cases, the reports concerned mostly patients previously treated for CNS lesions, but even PFS and OS data presented in those studies seem encouraging.

After the first 18 patients, we did not record any brain hemorrhagic event. On the other hand, we did have some cases of life-threatening toxicities: two patients (see Table II) had cerebral ischemia, not fatal, but with a severe impairment of neurological functions, which forced us to prematurely stop therapy. We also had a case of pulmonary embolism with non-severe consequences for the patient, but the therapy was suspended for caution. There are data that show a high risk of embolism in patients with malignant glioma (11), whilst bevacizumab could be involved in the pathogenesis of ischemia (12).

In conclusion, a front-line therapy with bevacizumab for brain metastases from adenocarcinoma appears feasible and led to very promising efficacy data.

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