Bevacizumab and Glioblastomas, a Single-Centre Experience: How Disease History and Characteristics May Affect Clinical Outcome

FABLE ZUSTOVICH[1], GIUSEPPE LOMBARDI[1], DAVIDE PASTORELLI[1], PATRIZIA FARINA[1], LARA FURINI[1], RENZO MANARA[2], MAURIZIA DALLA PALMA[1], ANTONINO ROTILIO[2], ORNELLA NICOLETTO[1] and VITTORINA ZAGONEL[1]

[1]*Oncologia Medica 1- Istituto Oncologico Veneto, IRCCS, Padova, Italy;*
[2]*Dipartimento di Neurochirurgia, Azienda Ospedaliera di Padova, 35128 Padova, Italy*

Abstract. *Background: In 2009, bevacizumab, a monoclonal antibody to vascular endothelial growth factor, received accelerated approval by the United States Food and Drug Administration for the treatment of glioblastoma, based on its high response rate (RR) and 6-month progression-free survival (PFS-6). However, time to progression and overall survival (OS) were disappointing. Since 2008 have been data collected evaluating the safety and efficacy of bevacizumab in patients with relapsed malignant gliomas. Patients and Methods: This is a retrospective review of adult patients with recurrent malignant gliomas treated with bevacizumab at a dose of 10 mg/kg every 14 days; some patients were also treated with irinotecan at a dose of 125 mg/m^2 every 14 days. Patients were evaluated for side-effects and clinical outcomes of response, progression and survival. Results: Ten patients received bevacizumab and nine patients received the combination with irinotecan. Both single-agent bevacizumab and combination treatment were well-tolerated. RR was of 28% with no complete responses, PFS-6 was 20% and OS was 4.5 months (95% confidence interval: 3.07-5.98 months). Conclusion: Although well-tolerated, the efficacy of bevacizumab was somewhat disappointing, possibly due to the high rate of secondary high-grade gliomas in the studied patient cohort and the late use of bevacizumab in the course of the disease.*

Standard treatment of glioblastoma (GBM) is currently based on the sequence of surgery, adjuvant radiotherapy with concomitant temozolomide followed by adjuvant temozolomide for 6 months (1). The five-year follow-up of data from the phase III trial published by Stupp *et al*. in 2005 showed that 5-10% of patients treated with temozolomide are long-term survivors (2). Nevertheless, for the majority of patients who relapse there is no widely accepted standard treatment. GBM is one of the most highly vascular carcinomas and targeting angiogenesis is a rational approach to therapy. In the United States, bevacizumab, an anti-vascular endothelial growth factor antibody, has been approved for the treatment of relapsed malignant gliomas since May 2009 on the basis of very promising phase II data in the recurrent setting. Kreisl *et al*. treated 45 heavily pre-treated GBM patients with bevacizumab at a dose of 10 mg/m^2 (3). The Mcdonald's response rate (RR) was 35% (calculated from on magnetic resonance imaging scans), reaching 71% when Levin's criteria were used (subjective assessment of the patient), with a 6-month progression-free survival (PFS-6) of 29%. In the same study, 19 patients progressing during bevacizumab were treated with the addition of irinotecan without any significant further benefit. Bevacizumab monotherapy appeared to be a well-tolerated treatment without significant toxicity (3). In another phase II study published by Friedman *et al*., 167 patients were randomised to receive bevacizumab alone or bevacizumab and irinotecan. RR was of 28.2% and 37.8% with a PFS-6 of 42.6% and 50.3%, respectively; these differences were not statistically significant (4). In that study, the survival curves were similar suggesting the lack of benefit when adding irinotecan to bevacizumab. On the basis of these encouraging preliminary efficacy and safety data, relapsed GBM patients have been treated with bevacizumab in the host institute (Istituto Oncologico Veneto, Padova, Italy) since May 2008. The present study retrospectively reports on the experience of the host institute using this agent in patients with recurrent malignant glioma.

Correspondence to: Fable Zustovich, Istituto Oncologico Veneto - IRCCS, Via Gattamelata n. 64, 35128 Padova, Italy. Tel: +39 3479775504, Fax: +39 498215904, e-mail: fable.zustovich@ioveneto.it

Key Words: Chemotherapy, malignant, glioma.

Patients and Methods

Pre-treated adult patients with temozolomide refractory and progressive high-grade malignant gliomas, not eligible for further surgery and/or radiotherapy, were treated with bevacizumab. Depending on ECOG performance status and number of prior chemotherapy regimens, a combination of bevacizumab plus irinotecan was used in a subset of patients. Patients with prior low-grade gliomas who evolved to high grade were also evaluated. The only factors leading to exclusion from treatment were uncontrolled hypertension, active infections and non-healing wounds.

Bevacizumab was infused intravenously for 90 minutes at a dose of 10 mg/kg of body weight with or without irinotecan at a dose of 125 mg/m^2 of body surface, every 14 days. The duration of each cycle was 28 days. Patients treated earlier in this series who were on enzyme-inducing antiepileptic drugs were not treated with higher dose of irinotecan because they were heavily pre-treated with prior chemotherapy and because the merging data about the lack of benefit when adding irinotecan to bevacizumab in patients with bevacizumab refractory disease (3), patients treated later on in the series received bevacizumab alone. Standard premedication with antiemetic and antiallergic prophylaxis with 3 mg granisetron, 20 mg dexamethasone and 8 mg chlorpheniramine maleate was also administered. If no bevacizumab-induced allergic reaction was detected, the time of infusion was shortened to 60 and then to 30 minutes. Haematological toxicity in asymptomatic patients was evaluated the day before the administration of the subsequent chemotherapy cycle.

Disease evaluation was assessed within 3 weeks before the beginning of treatment and then every two months or four bevacizumab administrations. Toxicity was assessed prior to each cycle and treatment was continued until disease progression or unacceptable toxicity. Since the present study was a single institutional study, follow-up of patients was regular and well-controlled except for one patient who was lost to follow-up and was excluded from the final analysis. Macdonald's criteria were used to evaluate response and MRI images with FLAIR contrast were used in some cases to exclude infiltrative and non contrast-enhancing disease progression. PFS and overall survival (OS) were calculated from the start of therapy with bevacizumab until progressive disease or death. The Kaplan-Meier method was used to estimate the survival curves. Data analyses were performed using the SPSS 15 (SPSS Inc. Chicago, IL, USA).

Results

Patient characteristics. From May 2008 to May 2010, 20 consecutive patients were enrolled. As mentioned earlier, one patient was lost to follow-up and was not included in the series. Concomitant illnesses were not significant. Eleven patients had undergone surgery for a second time; six patients had second- and third-line chemotherapy (mostly fotemustine and temodal plus cisplatin); five patients had carmustine wafers (Gliadel®; Eisai Inc.,Woodcliff Lake, NJ, USA) implanted during first or second surgery; eight patients had glioblastoma as the evolution of a low-grade glioma; nine patients received concomitant irinotecan.

Table I. *Overall toxicity during all treatment courses by type and grade.*

Type	Grade 1-2 n=19	Grade 3-4 n=19
Granulocytopenia	2*	-
Anaemia	2*	-
Thrombocytopenia	2*	-
Anorexia	2	-
Nausea	1	-
Constipation	2	-
Diarrhoea	1*	-
Somnolence	1	-
Fatigue	3	-
Infection	-	1#
Hypertension	2	-
Proteinuria	1	-

*All pateints receiving CPT11; #patient receiving bevacizumab alone.

Overall toxicity. All 19 patients where evaluable for toxicity. A total of 113 cycles were administered, with a median of 4 (range: 2-16) cycles for each patient. Toxicity (Table I) was mild, mostly haematological in patients receiving the combination of bevacizumab and irinotecan. One patient had osteomyelitis of the right tibia of uncertain origin and treatment was suspended after the first administration of bevacizumab.

Objective responses and survival. A total of 18 out of 19 patients were evaluable for response. Five patients (28%) had a partial response, 6 patients had stable disease (33%) and 7 had disease progression. The disease control rate was of 61%.

At the time of the analysis, 5 out of the 18 evaluable patients had progressed and 11 had died. Median time to progression was 3 months (95% confidence interval: 1.8-4.1 months), PFS-6 was of 20% and OS was 4.5 months (95% confidence interval: 3.07-5.98 months).

Discussion

The publication of preliminary data of bevacizumab in patients with recurrent GBM was received with great enthusiasm among neuro-oncologists. In single arm, non-randomised studies, treatment has been associated with an RR of 25-57% and a PFS-6 of 30-50% in patients with relapsed GBM, which is an improvement in comparison to the palliative chemotherapy available (Table II).

Similar to other studies, the present study was interested in assessing the use of bevacizumab in recurrent malignant glioma. Despite its retrospective design, the present study had the advantage of close and uniform follow-up in the majority of patients. The study confirmed the very good toxicity profile of bevacizumab as shown in Table I. However, compared to previous reports, less encouraging efficacy results were

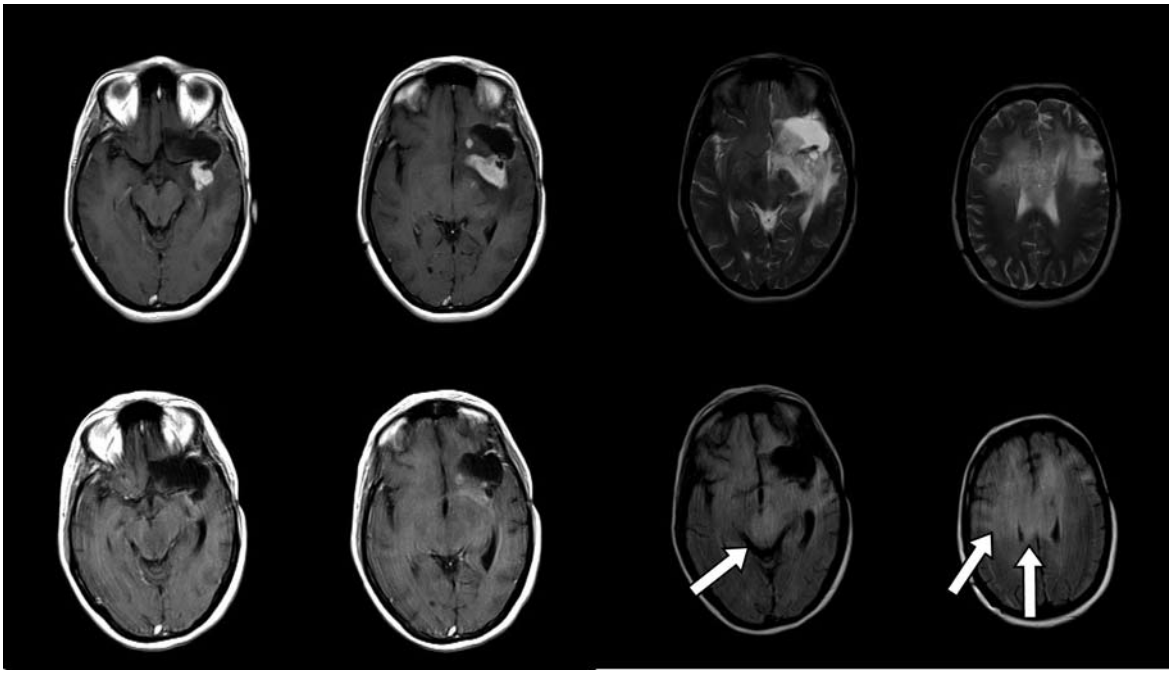

Figure 1. *MRI of a patient with bevacizumab-induced 'pseudo response', before (above) and after (below) bevacizumab: T_1-weighted gadolinium-enhanced (left two columns) and FLAIR (right two columns) images showing disease progressing (arrows) in the brain stem and temporal lobe.*

Table II. *Comparison of the results from the present study with those from published phase II studies.*

Study	Treatment	Number of patients	RR (%)	Median PFS (months)	PFS-6 (%)	OS (months)
Kriesl *et al*. (3)	Bevacizumab	48 (all GBM)	35	3.7	29	7.2
Friedman *et al*. (4)	Bevacizumab	82 (all GBM)	28	NA	42.6	9.2
Raizer *et al*. (5)	Bevacizumab	61	25	3.9	32	6.6
Stark-Vance (6)	Bev.+ irinotecan	21	43	NA	NA	NA
Vredenburgh *et al*. (7)	Bev.+ irinotecan	35 (all GBM)	57	5.5	46	9.7
Friedman *et al*.(4)	Bev.+ irinotecan	85 (all GBM)	38	NA	50.2	8.7
Gilbert *et al*. (8)	Bev.+ irinotecan	57 (all GBM)	NA	NA	37	NA
Present study	Bevacizumab and Bev.+irinotecan	19	28	3	20	4.5

NA: Not available.

observed with a RR of 28%, a PFS-6 of 20% and an OS of 4.5 months (Table II). These findings may be due to several reasons. The patients in the present study were heavily pre-treated: a proportion of patients were re-treated with chemotherapy and with further surgery after relapse and patients received bevacizumab treatment late in their disease history. In fact, the time from diagnosis to bevacizumab treatment was 17.2 months and the median OS of the patients from initial diagnosis of GBM was more than 23.4 months. These findings are in marked contrast to the reported phase II studies that included only patients at first relapse (Table III). Moreover, since 8 out of 19 patients had secondary GBM that transformed from a preceding low-grade or anaplastic glioma, molecular characteristics such as early p53 loss and PDGFR overexpression (9), may have rendered their response to anti-angiogenic therapy less likely. Consequently, these patients may have exhibited a poorer prognosis in comparison with those with primary GBM. Due to the small number of patients in the present study, the role of potential prognostic factors or the effect of concomitant administration of irinotecan on clinical outcome were not evaluated. No patient was treated with the sequence of bevacizumab and then bevacizumab plus irinotecan at the time of progression, mostly due to studies demonstrating that this strategy lacks any benefit for the patient (3).

Several interesting observations emerged from the disease evaluations using MRI images. Some patients showed a response on contrast-enhanced T1-weighted MRI with evidence of progression on FLAIR MRI (Figure 1). Patients with these findings had worsening of PS and neurological status and died few weeks later. This bevacizumab-induced 'pseudoresponse' on contrast-enhanced T1-weighted MRI has now been recognised as a challenge in the evaluation of bevacizumab and new radiographic criteria have been proposed (10).

In conclusion, not surprisingly, the effect of bevacizumab on the treatment of recurrent malignant glioma was not as encouraging as reported in other phase II studies. This is likely due to patient selection since the patients of the present study were heavily pre-treated and far along in their disease trajectory. Nevertheless, the findings of the present study represent interesting new knowledge about the use of bevacizumab in GBM and suggest that the efficacy may depend on the disease history and characteristics.

References

1 Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, Belanger K, Brandes AA, Marosi C, Bogdahn U, Curschmann J, Janzer RC, Ludwin SK, Gorlia T, Allgeier A, Lacombe D, Cairncross JG, Eisenhauer E and Mirimanoff RO: Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med *352*: 987-996, 2005.

2 Stupp R, Hegi ME, Mason WP, van den Bent MJ, Taphoorn MJ, Janzer RC, Ludwin SK, Allgeier A, Fisher B, Belanger K, Hau P, Brandes AA, Gijtenbeek J, Marosi C, Vecht CJ, Mokhtari K, Wesseling P, Villa S, Eisenhauer E, Gorlia T, Weller M, Lacombe D, Cairncross JG and Mirimanoff RO: Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma patients in a randomised phase II study: 5-year analysis of the EORTC-NCIC Trial. Lancet Oncol *10*: 459-466, 2009.

3 Kreisl NT, Kim L, Moore K, Duic P, Royce C, Stroud I, Garren N, Mackey M, Butman JA, Camphausen K, Park J, Albert PS and Fine HA: Phase II trial of single-agent bevacizumab followed by bevacizumab plus irinotecan at tumor progression in recurrent glioblastoma. J Clin Oncol *27(5)*: 740-745, 2009.

4 Friedman HS, Prados MD, Wen PY, Mikkelsen T, Shiff D, Abrey LE, Yung KWA, Paleologos N, Nicholas MK, Jensen R, Vredemburgh J, Huang J, Zheng M and Cloughesy T: Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. J Clin Oncol *27(28)*: 4733-4740, 2009.

5 Raizer JJ, Grimm S, Rice L, Muro K, Chandler J, Tellez C, Mellot AL, Newman S, Nicholas MK and Chamberlain M: A phase II trial of single-agent bevacizumab given every 3 weeks for recurrent malignant gliomas. J Clin Oncol *27(15s)*: 2044, 2009.

6 Stark-Vance V: Bevacizumab and CPT-11 in the treatment of relapsed malignant glioma. Neuro Oncol *7(3)*: 369, 2005.

7 Vredenburgh JJ, Desjardins A, Herndon JE 2nd, Marcello J, Reardon DA, Quinn JA, Rich JN, Sathornsumetee S, Gururangan S, Sampson J, Wagner M, Bailey L, Bigner DD, Friedman AH and Friedman HS: Bevacizumab plus irinotecan in recurrent glioblastoma multiforme. J Clin Oncol *25(30)*: 4722-4729, 2007.

8 Gilbert MR, Wang M, Aldape K, Lassman A, Sorensen AG, Mikkelson T, Groves M, Werner-Wasik M, Regine W and Mehta M: RTOG 0625, A phase II study of bevacizumab with irinotecan in recurrent glioblastoma (GBM). J Clin Oncol *27(15s)*: 2011, 2009.

9 Maher EA, Brennan C, Wen PY, Durso L, Ligon KL, Richardson A, Fhatry D, Feng B, Sinha R, Louis DN, Quackenbush J, Black PM, Chin L and DePinho RA: Marked genomic differences characterize primary and secondary glioblastoma subtypes and identify two distinct molecular and clinical secondary glioblastoma entities. Cancer Res *66(23)*: 11502-11513, 2006.

10 Wen PY, Macdonald DR, Reardon DA, Cloughesy TF, Sorensen AG, Galanis E, DeGroot J, Wick W, Gilbert MR, Lassman AB, Tsien C, Mikkelsen T, Wong ET, Chamberlain MC, Stupp R, Lamborn KR, Vogelbaum MA, van de Bent MJ and Chang SM: Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. J Clin Oncol *28(11)*: 1963-1972, 2010.

Received September 20, 2010
Revised October 26, 2010
Accepted October 28, 2010