Bevacizumab and etoposide combination chemotherapy in patients with recurrent malignant gliomas who failed bevacizumab

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Abstract

Bevacizumab is the current standard of care treatment for recurring malignant glioma patients. However, most of the tumors become resistant to bevacizumab, and there is no standardized, effective chemotherapy for the malignant glioma patients after bevacizumab failure. Retrospective chart review was performed in order to identify the malignant glioma patients treated with oral, metronomic etoposide in combination with bevacizumab after being diagnosed with progressive disease while on bevacizumab. This review was approved by the Institutional Review Board (IRB) of the University of California, Irvine. Six malignant gliomas patients met the inclusion criteria. The median progression-free survival (PFS) for the anaplastic astrocytoma (AA) patients was eight months, and the overall survival was 28 months. The two Glioblastoma Multiforme (GBM) patients showed tumor progression after four to eight weeks of treatment with bevacizumab and etoposide, and died within four months of beginning the etoposide/bevacizumab regimen. In this limited study, patients with AA demonstrated prolonged control on combination treatment with bevacizumab and oral etoposide, despite initial tumor progression on bevacizumab. These results may warrant further investigation on a prospective clinical trial of this combination in AA patients who developed resistance to bevacizumab.

Introduction

Despite recent advances in neuro-oncology, the prognosis of malignant gliomas remains poor, and the treatment options are limited.[1] After the standard therapy of surgical resection and radiation concomitant with temozolomide, great majority of these tumors recur.[2] Treatment with the anti-angiogenesis agents revealed promising results for patients with recurrent gliomas,[3,4] and bevacizumab has become the most accepted standard second-line therapy for recurrent GBM and recurrent AA patients. Unfortunately, the overwhelming majority of these patients still relapse, and there is currently no uniformly accepted effective therapy for bevacizumab failure. The published median PFS for GBM patients that receive salvage chemotherapy such as dasatinib,[5] irinotecan[6] or various other agents (temozolomide, carmustine, perifosine, gimatecan or carboplatin)[7] is only 1-2 months, while the overall survival (OS) for the same patients is 2.5- 5 months. The PFS and OS are less well characterized for AA patients who relapsed on bevacizumab. In a small, mixed, patient population (both grade IV and grade III tumors), the continuation of bevacizumab together with third and fourth line chemotherapy options including carmustine, lomustine, etoposide, temozolomide and erlotinib resulted in a median time to radiologic progression of only 7 weeks. No prospective data are available on the survival of AA patients after bevacizumab failure.

Etoposide (VP-16) is a topoisomerase II inhibitor.[8] The interest on etoposide as a treatment for malignant gliomas[9] was refueled by the increased understanding of the importance of angiogenesis in malignant glioma resistance to treatment.[10] Etoposide can be administered on protracted, daily schedules, a metronomic administration which potentially targets proliferating tumor endothelium.[11] Metronomic etoposide therapy showed activity in patients with malignant gliomas recurrent after radiation and nitrosurea-based chemotherapies, with a PFS of 7.5 weeks for GBM and 9.1 weeks for AA.[12] However, the metronomic chemotherapy with etoposide in combination with bevacizumab had similar anti-tumor activity and produced more toxicity than bevacizumab monotherapy in malignant glioma patients who had recurrent disease after radiation or chemotherapy but were naïve to bevacizumab.[13]

No study has been reported to date on patients with recurrent malignant gliomas who failed bevacizumab, and were treated with bevacizumab and oral etoposide at the time of bevacizumab failure. Rapid clinical deterioration after discontinuing the bevacizumab is common, presumably because of rebound angiogenesis.[14] Therefore, we sought to retrospectively evaluate if the metronomic etoposide addition to bevacizumab can improve patient's outcome by potentially targeting the vasculature re-growth in the tumor areas which have escaped Vascular Endothelial Growth Factor (VEGF) blockade.

Case Report

This study was approved by the IRB at University of California, Irvine and included patients with histologically confirmed malignant gliomas who developed tumor progression on bevacizumab, and who at the time of bevacizumab failure were started on etoposide (50mg/m^2 for 21 out of 28 days). Bevacizumab was continued at 10 mg/kg every two weeks. The response was measured by Magnetic Resonance Imaging (MRI) based on Macdonald criteria (with both contrast-enhanced and FLAIR imaging measurements),[15] Magnetic Resonance Spectroscopy (MRS) and brain tumor biopsy if clinically indicated at the time of progression.

Results

Patient characteristics

Six patients were identified, four diagnosed with AA and two with GBM. All of them were men, with a median age of 54 (range 45-65) (Table 1). Karnofsky performance status ranged from 40-90 (median 65). Their treatment consisted of fractionated radiotherapy concomitant with daily temozolomide for 6 weeks, followed by temozolomide administered at 150-200 mg/m^2 for five days every 28 days by the Stupp protocol.[2] At the time of their first tumor progression, all patients were started on bevacizumab, either alone (patient #1) or in combination with irinotecan (patient #5). The

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Table 1. Patients characteristics. Six patients with malignant glioma resistant to bevacizumab, which were treated with etoposide-bevacizumab at the time of relapse.

Patient	Sex/Age	Histology (WHO grade)	Tumor location	KPS	Surgery extent	Initial therapy IXRT and tomozolomide	PFS on first-line chemotherapy (tomozolomide)	Second-line chemotherapy/ PFS	PFS on third-line chemotherapy (etoposide - Bevacizumab)	OS after first Bevacizumab failure
1	M/48	AA (III)	Left frontal lobe	90	Bx	Y	2 months (progressed after XRT+TMZ)	Irinotecan-Bevacizumab 14 months	8 months	20 months*
2	M/57	AA (III)	Left medial temporal lobe	80	Bx	Y	2 months (progressed after XRT+TMZ)	Bevacizumab 2 months	8 months	36 months*
3	M/45	AA/AO (III)	Left thalamus	90	Bx	Y	5 months	Irinotecan-Bevacizumab 9 months	6 months	17 months
4	M/50	AA (III)	Left temporal lobe	60	STR	Y	10 months	Irinotecan-Bevacizumab 11 months	11 months	20 months
5	M/64	GBM (IV)	Right temporal lobe	40	STR	Y	6 months	Irinotecan-Bevacizumab 4 months	1 month	3 months
6	M/65	GBM(IV)	Right parietal lobe	50	STR	Y	6 months	Irinotecan-Bevacizumab 3 months	2 months	4 months

M, Male, Bx, Biopsy; STR, Subtotal resection; XRT, Focal beam radiation; TMZ, Temozolomide, *Alive

tumor response was monitored with MRIs every 6 weeks while they were on Bevacizumab. At the time of second progression, all the patients were started on metronomic etoposide and continued on bevacizumab. Those being treated with irinotecan had this medication discontinued.

Response

Two patients with recurrent AA are still alive, stable after 8 and respectively 11 months of etoposide-bevacizumab, and off chemotherapy. All AA patients were evaluated for best radiographic response, which was partial in 3 patients and stable in 1 patient (for 6 months) giving a 75% radiographic response rate. The median PFS is 8 months (6-11 months), and their OS to this point is 28 months. One of patients - which developed progressive tumor after eleven months of bevacizumab-irinotecan combination (Figure 1C and 1D) - has remained stable after 11 cycles of bevacizumab and oral etoposide regimen for his progressive AA (Figure 1E and 1F).

The two GBM patients showed no response to the bevacizumab and etoposide combination. Their time to progression was of 1-2 months, and their OS was 3-4 months.

Toxicity

The patients tolerated the treatment well. The most common side effects were neutropenia, thrombocytopenia and mucositis (Table 2). Two patients had delays in restarting their etoposide due to prolonged thrombocytopenia, and their

Table 2. Etoposide-bevacizumab related adverse events (number of events.)

Toxicity	Grade 1	Grade 2	Grade 3
Thrombocytopenia	0	1	1
Neutropenia	0	1	1
Mucositis	0	1	0

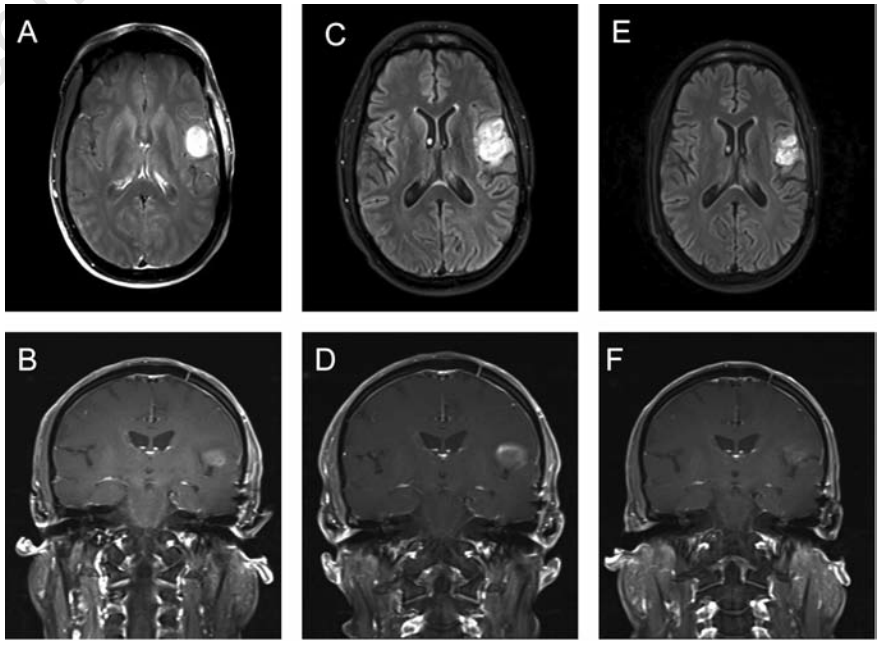

Figure 1. Treatment response (patient #4). A,B) First progression after radiation and Temozolomide; C,D) tumor progression on bevacizumab and irinotecan; E,G) tumor response after 11 months of etoposide-bevacizumab.

subsequent dose was adjusted to an alternating schedule between 50 mg and 100 mg.

Discussion

The findings of this small, retrospective pilot study suggest the combination regimen of bevacizumab and oral low-dose etoposide show very promising results in a small group of patients with a diagnosis of AA who failed bevacizumab based treatment, but had no beneficial effect for patients with GBM. The treatment is well tolerated. The most common side-effect is thrombocytopenia.

Several factors could account for the potential positive effects of etoposide in this patient group that are already resistant to bevacizumab. Bevacizumab failure has been reported to be associated with increased invasion of non-enhancing tumor[7] and preliminary reports in both human tumor specimens and murine models suggest the involvement of the matrix metalloprotease 2 (MMP2).[16] Etoposide has been reported in other models to reduce the amount of MMP-2 secreted protein[17] and hence might work by counteracting the increased MMP2 production caused by bevacizumab. In addition, etoposide treatment also activates tumor metastasis suppressor genes such as KAI1, and results in significant decreased invasion in multiple cancer cell lines.[18]

Another common finding in patients with progressive malignant glioma after bevacizumab treatment is the appearance of extensive hypoxic zones surrounding areas of necrosis.[16] In malignant glioma, adaptation to hypoxia is mediated by intense expression of the transcriptional activator hypoxia-inducible factor 1α (HIF-1α).[19] Etoposide inhibits the accumulation of HIF-1α in lung cancer cell lines by a proteasome dependent mechanism, and furthermore daily additions of etoposide even at a much lower concentrations, was more effective than a single treatment-supporting our strategy of metronomic administration.[20]

While absence of effect in only two GBM patients might be attributable to statistical aberration that would be diluted out in a larger study, a major unanswered question is why the metronomic etoposide appears in our study to be effective only in AA patients and not in GBM patients. That our findings might be correct would seem to be supported by previously published data on the use of etoposide for recurrent gliomas[12] where prolonged metronomic therapy showed better results for patients with recurrent AA and AO than for patients with GBM. Furthermore, a recently published Phase II study of metronomic chemotherapy (etoposide or remozolomide) with bevacizumab after progression on bevacizumab therapy failed to find any benefit for this therapy in the GBM patient population.[21]

The present small retrospective study suggests activity of the combination of bevacizumab and oral etoposide treatments on patients with recurrent AA who relapsed on a first bevacizumab regimen. This promising results warrant further investigation in a larger prospective study of this patient population where no effective treatment is available.

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