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Review of Bevacizumab and Etoposide Combination Efficacy and Safety in Patients with Recurrent Malignant Gliomas who Have Failed Bevacizumab

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Abstract

Despite recent advances in the treatment of malignant gliomas (World Health Organization grade III and grade IV tumors- Glioblastoma Multiforme, Anaplastic Astrocytoma and Anaplastic Oligodendroglioma), the overall prognosis remains poor. Tumor recurrence in malignant glioma is inevitable, and associated with reduced overall survival (OS). Bevacizumab is approved for use in progressive GBM as a second line treatment, and is associated with improvements in progression free survival (PFS). However, all GBM patients eventually recur on bevacizumab therapy, with a very short OS after bevacizumab failure. No FDA- approved therapy is available for this clinical setting. Etoposide crosses the blood-brain barrier and has activity in recurrent malignant gliomas. The use of bevacizumab with etoposide in recurrent malignant gliomas in the setting of bevacizumab resistance is evaluated in this review. Bevacizumab and etoposide combined therapy is associated with radiographic response and effectiveness in selected patients.

The Review In Brief:

- In recurrent malignant gliomas previously treated with anti-angiogenic agents, the use of etoposide with bevacizumab is safe and clinically active in a selected group of patients.
- Etoposide and bevacizumab can be used in a variety of combinations for recurrent GBM as salvage chemotherapy.

Questions For Further Research:

- In the recurrent setting, the optimal combination of chemotherapy regimen is not yet established and new treatments are needed.
- The use of older conventional chemotherapy use in combination with newer anti-angiogenic treatments should be further explored.

Background

Glioblastoma multiforme (GBM) is the most common primary malignant brain tumor in adults with an incidence rate of 3.17 per 100,000 person-years [1]. Despite multiple recent advances in the treatment of malignant gliomas, the prognosis for recurrent malignant gliomas remains poor with 2-year overall survival of nearly 12% in population studies [1]. The use of surgical resection followed by radiation and concomitant temozolomide chemotherapy has been well established as first-line therapy and is associated with a median survival of 14.6 months and 2-year overall survival of 27%[2, 3]. Due to the limited ability of chemotherapies to cross the blood-brain barrier, multidrug resistance proteins, and genetic and epigenetic heterogeneity, malignant gliomas are among the most challenging tumors to treat.

Vascular endothelial growth factor (VEGF) has been shown to be an important factor in tumor angiogenesis and is expressed in human gliomas [4-6]. Levels of VEGF

correlate in increased microvascular density and are seen more frequently in GBM than lower grade astrocytomas [5, 7, 8]. VEGF-A is mediated by VEGF-receptor -2 (VEGFR-2) and is the key mediator in malignant glioma angiogenesis. Inhibition of VEGF in GBM has been shown to improve survival[9]. Bevacizumab (Avastin) is a humanized murine immunoglobulin (Ig) G_1 monoclonal antibody that binds to and inhibits the activity of VEGF, preventing the interaction and activiation of VEGF receptor tyrosine kinases VEGFR-1 and VEGFR-2 [10, 11].

At time of tumor recurrence, the use of bevacizumab has been associated with improved clinical performance and a superior 6-month progression-free survival (PFS-6) of 42-50% [12, 13]. The use of bevacizumab alone or in combination with CPT-11 (irinotecan, Camptosar) yielded similar overall survival times of 9 months [13]. The significant objective response and favorable PFS seen in this phase II study resulted in U.S. Food and Drug Administration accelerated approval of bevacizumab for the treatment of recurrent GBM patients in 2009.

The optimal treatment of recurrent malignant gliomas that have failed bevacizumab therapy is not well established [14, 15]. The prognosis in GBM after failure of bevacizumab is dismal with most patients developing progressive disease within 1 to 4 months and survival of 4 to 7 months after start of therapy in prospective studies.[16-18] Bevacizumab use in the recurrent setting of high-grade gliomas previously treated with anti-angiogenic agents was evaluated by Scott et al [19]. The use of bevacizumab in 24 patients previously treated with various VEGF receptor

tyrosine kinases produced radiographic response (PR) in 21% and stable disease in 58%. Bevacizumab salvage therapy resulted in a median time to progression (TTP) of 8 weeks, and median OS of 5.2 months after onset of therapy. As expected, the radiographic response and median TTP were less robust as compared to the initial anti-VEGF treatment.

In patients experiencing tumor progression while on bevacizumab therapy, surgery with further tumor resection is complicated by wait times of up to four weeks to allow for clearance of drug, and minimize the risk of poor wound healing from impaired angiogenesis [20, 21]. The importance of preventing wound breakdown is underscored by resultant CSF leaks and wound infections. In a study investigating the impact of bevacizumab on wound healing, significantly more patients who received preoperative bevacizumab developed healing complications than non-bevacizumab treated patients, 35% vs. 10%, respectively[20]. In the same retrospective study, risk of dehiscence increased from 12% in non-bevacizumab pre-operatively treated patients to 50% in those receiving bevacizumab prior to craniotomy. The multiple surgical complications after bevacizumab use provide support for the need for further salvage treatment options in recurrent malignant gliomas. Decisions for surgical tumor debulking following bevacizumab use should be weighted against the risks of wound healing complications and infections.

Etoposide

Etoposide (VP-16, VePesid) is a semi-synthetic derivative of podophyllotoxin, which acts as a cell cycle-specific agent blocking cells in the late S-G_2 phase.

Etoposide may be taken orally or intravenously and readily crosses the blood-brain barrier where it causes tumor DNA damage via strand breakage involving inhibition of topoisomerase II [22]. Sensitivity to etoposide correlates to expression of the topoisomerase II (Topo II) enzyme in cell lines [23]. Acute toxicities associated with etoposide include nausea, vomiting and hypotension, while delayed toxicity includes alopecia, and bone marrow depression.

The activity of etoposide alone in recurrent supratentorial malignant glioma was described by Tirelli et al and Fulton et al [24, 25]. The Italian group described the use of etoposide given intravenously days 1-5, dose escalated as tolerated, and repeated every 3 weeks in 22 patients. The Italian group observed clinical or radiologic response in 33% of patients.

In a different study, etoposide was given orally in a prolonged daily dosing as continuous therapy in order to achieve more uniform cell-cycle inhibition among those dividing cells [25]. Forty-six patients evaluated in this study of which 46% were GBM, and 20% were anaplastic oligodendrogliomas. Treatment was well tolerated. Patient outcome analysis revealed a median time to progression (TTP) of 8.8 weeks and median survival of 24.5 weeks. Radiologic objective response (CR+PR) was seen in 18% and total response (CR+PR+SD) was seen in 42%. Among those responding to

treatment or stable, outcomes were improved with a median TTP was 16 weeks, and median survivals of 36-45 weeks.

Etoposide Use in Combined Regimens

Temozolomide and Etoposide

Data from a Phase I clinical trial by Korones et al evaluated the use of temozolomide and escalating doses of oral etoposide in 29 recurrent malignant glioma patients [26]. In this study, glioblastoma and gliosarcomas (10%) comprised 76% of the patient population with the remaining 24% of patients having either anaplastic astrocytoma or anaplastic oligoastrocytomas. In this Phase I trial, the informal outcomes to temozolomide and etoposide yielded a radiographic response rate of 7% and a total response of 45%. The median duration of response was 4 months. Table 1 summarizes recurrent studies containing etoposide combination therapy (Table 1).

Carboplatin and Etoposide (CE Regimen)

The combination of carboplatin and etoposide have been utilized by various investigators to capitalize on the synergistic activity of these compounds [27]. In this phase II study by Jeremic et al., 38 patients received Carboplatin days 1-5, etoposide days 1-5 repeated every 4 weeks. Patients were 79% GBM and 21% anaplastic astrocytoma, and tended to be heavily pretreated. The radiologic response rate was

21%, while total response rate was 53%. Median time to progression was 14 weeks and median survival time was 43.5 weeks.

The use of etoposide and carboplatin was evaluated by Watanabe et al. in a phase II study of 28 recurrent anaplastic astrocytoma and GBM patients [28]. The regimen consisted of intravenous carboplatin day 1, and etoposide days 1-5, and repeated every 6 weeks. Radiographic response was seen in 14% of GBM and 36% of AA patients, with total response seen in 57% of GBM and 79% of AA patients. The mean duration of the effect of treatment in those patients with total response was 9.3 months in AA and 4.1 months in GBM patients. The median survival time was 38.5 months and 13 months for AA and GBM, respectively.

The Italian group of Franceshci et al. investigated the use of etoposide and carboplatin in a phase II study of 30 recurrent GBM or AA [29]. Carboplatin was given intravenously days 1-3, and etoposide on days 1-3 every 4 weeks to a maximum of 12 cycles. Among the 25 GBM patients, the radiographic response rate was 24% and a total response rate of 64%. For GBM and AA patients, the overall radiographic response rate was 30% and total response rate was 70%. The overall median time to progression was 4 months, with a PFS-6 of 33.3% and PFS-12 of 26.7%. The median time to progression was 3 months in the GBM subgroup, with a PFS-6 of 20%. The overall median survival time was 10 months, with the GBM subgroup median survival time of 9 months. Response to treatment in this study may have been affected by the high performance status in this group of patients who were not heavily pretreated.

Ifosfamide, Carboplatin and Etoposide (ICE Regimen)

In an early Phase II study by a French group, recurrent supratentorial malignant gliomas were treated with ifosfamide, carboplatin and etoposide (ICE) in 36 patients [30]. Investigators hoped to exploit the synergistic effects of etoposide, cisplatin and the alkylating agent ifosfamide, a combination regimen which has demonstrated a high therapeutic index in a variety of malignancies. Doses were increased according to hematological tolerance from ifosfamide days 1-3, carboplatin days 1-3, etoposide days 1-3, and repeated every 4 weeks. This study resulted in a favorable objective radiologic response of 28 % and a total response of 53%. The regimen demonstrated a median time to tumor progression of 13 weeks, and a median survival of 29 weeks. Grade III and IV hematologic toxicities were seen in 42% of patients and resulted in one death from neutropenic sepsis.

A Phase II study of the ICE regimen was performed by the Japanese group in forty-two GBM patients at time of first recurrence [31]. Dosing for this study was more conservative than the Sanson study, consisting of ifosfamide days 1-3, carboplatin day 1, etoposide days 1-3, every 6 weeks. The study revealed an objective response of 25% and a total response of 50%. The ICE regimen yielded a median 6-month progression-free survival of 35%, a median PFS of 17 weeks, and a median survival time of 10.7 months. Toxicities consisted mainly of alopecia, and Grade III and IV hematologic toxicities in 17% of patients.

The use of etoposide as part of the ICE regimen in recurrent malignant gliomas was evaluated by the German group in 13 patients [32]. Patients received ifosfamide day 1-3, carboplatin day 1, and etoposide day 1-3, in a 6-week cycle. Three patients had been pretreated with bevacizumab, and another 3 patients went on to receive bevacizumab as part of further treatments. The ICE regimen resulted in a median PFS of 2 months, and median OS of 5 months. Unfortunately, this regimen yielded no survivors at 6-months, however, the population was quite heterogenous and included 2 patients with KPS of $\leq$50.

Etoposide plus Anti-Angiogenic Agents in Recurrent Setting

The phase II study by Kesari et al. investigated the use of metronomic chemotherapy in recurrent malignant gliomas to assess whether continuous dosing would enhance disruption of the rapidly proliferating endothelial cells seen in angiogenesis [33]. This study utilized a combination of etoposide and cyclophosphamide as cytotoxic agents, and thalidomide and celecoxib as the anti-angiogenic agents in 48 patients. The patient population was heavily pretreated with a median of two prior recurrences. The radiologic objective response rate was 9% and the total response rate was 62.5%. The GBM patients in this series had a median PFS of 11 weeks, PFS-6 of 9%, and median OS of 21 weeks. The anaplastic glioma patients in this series performed better, as expected, with a median PFS of 14 weeks, PFS-6 of 26%, and median OS of 42 weeks. The nominal antitumor activity that was seen with this

metronomic regimen was thought to be possibly limited by the choice of anti-angiogenic agents used. Table 2 summarizes the recurrent studies containing etoposide + anti-angiogenic agents (Table 2).

Bevacizumab and Etoposide

The effectiveness and safety of bevacizumab with concurrent etoposide chemotherapy are the focus of this article. A review of the literature yields scarce data on the use of bevacizumab with etoposide alone or in combination with other agents and is summarized below.

In a phase II two-arm trial, Reardon et al. evaluated metronomic etoposide or metronomic temodar with bevacizumab to treat twenty-three GBM patients that recurred on bevacizumab therapy [17]. Although the 52% achieved stable disease radiographically, there were no objective responses. In this heavily pre-treated group, the PFS-6 was 4.4% and subsequently at interim analysis both the etoposide and temozolomide arms were closed due to failure to meet predetermined efficacy outcomes. The patients in this study represent a heavily pre-treated group, most with $\geq$2 previous instances of progressive disease prior to enrollment, and all patients had previously been treated with bevacizumab. Although both treatment arms were closed, the median PFS and median OS favored the etoposide group over the temozolomide group, 8.1 vs. 4.1 weeks, and 19 vs. 12.6 weeks, respectively. This

phase II study provides evidence of efficacy in recurrent malignant gliomas treated with etoposide who have failed bevacizumab therapy.

In a larger phase II open-label trial, Reardon et al. evaluated metronomic etoposide plus bevacizumab for recurrent malignant glioma in 59 patients [34]. Oral etoposide was given for 21 days every 28 days and bevacizumab was administered every 14 days. Patients were a heavily pretreated group with 26% of GBM patients having received $\geq$4 previous chemotherapeutic agents. The radiologic response rate was 23% and 24% among those patients with GBM, and anaplastic gliomas, respectively. The median PFS was 18 weeks for GBM and 24 weeks for anaplastic gliomas. The PFS-6 was 44.4% and 41% amongst GBM and anaplastic gliomas, respectively. The median OS was 46.4 weeks for GBM and 63.1 weeks for anaplastic gliomas in this study. Toxicities were common in this study; grade 4 toxicities consisted of neutropenia (8%), thrombosis (3%), hypertension (2%), and infection (2%).

Retrospectively, the use of bevacizumab and etoposide in study of malignant gliomas comprised mostly of anaplastic astrocytomas who had failed bevacizumab after initial therapy with radiation and temozolomide.[35] Among anaplastic astrocytomas the median PFS was 8 months and the median OS was 28 months. In this small study, the GBM patients fared worse with a median PFS of 1.5 months and median OS of 3.5 months. This regimen can be a useful treatment for recurrent GBM in patients with bevacizumab failure.

Bevacizumab, Carboplatin and Etoposide (ACE Regimen)

The Australian group described bevacizumab use combined with etoposide and carboplatin (ACE) in six recurrent GBM patients [36]. In this single institution retrospective analysis, the ACE regimen consisted of day 1, carboplatin area under the curve (AUC) 5 intravenously; days 1-3, etoposide intravenously; day 2, bevacizumab 10 mg/kg intravenously and this regimen was repeated every 3 weeks to a goal of 6 cycles. This regimen yielded a remarkable objective response rate (ORR) of 83%, although none of the patients had previously been treated with bevacizumab. The ACE treatment regimen yielded progression-free survival at 6 months (PFS-6) of 22%, median progression-free survival of 19 weeks, and a median overall survival (OS) of 29.9 weeks. Toxicities were mild in general with significant toxicities largely due to myelosuppression with this regimen. Thrombocytopenia was mild with no grade three or four toxicities. While no neutropenic fever was observed, grade 3 neutropenia was observed in two patients.

Discussion

We evaluate in this review of the literature the efficacy and safety of bevacizumab and etoposide in recurrent malignant gliomas who have failed previous bevacizumab therapy. In recurrent malignant previously treated with anti-angiogenic agents, the use of etoposide and bevacizumab is associated with total response rates of 52-62.5%, PFS-6 of 9%-44.4%, and median PFS of 8.1-24 weeks [33, 34, 36, 37].

Comparisons between these phase II studies is limited by the inherent differences in the patient populations among recurrent patients with respect to previous treatment regimens and number of recurrences.

In our experience at University of California Irvine, the combination of bevacizumab and etoposide has been well tolerated by patients with recurrent glioblastoma, with some neutropenia in this heavily pretreated group. The safety profile of the bevacizumab and etoposide combination is typically well tolerated. When bevacizumab and etoposide are given in combination after bevacizumab failure the toxicities have included grade three thrombocytopenia and neutropenia in up to .[35] Myelosuppression requiring dose modification of chemotherapy was not commonly seen with bevacizumab and etoposide combination treatment occurring in 28% of patients.[17] Toxicities increase when additional chemotherapies are added to bevacizumab and etoposide with dose reductions of cytotoxic chemotherapy needed in 36 - 83% of patients due to myelotoxicity.[16, 36]

The performance of etoposide regimens without anti-angiogenic agents can be weighed against those that contain bevacizumab. The range of radiographic response rates appear to be lessened, which is somewhat expected from the larger number of patients in this group treated with prior anti-angiogenic therapy. In these patients the reduced enhancement resultant from vascular “normalization” results in a dampening of the perceived radiographic response. The median PFS and PFS-6 data

compare well with those from patients not previously treated with anti-angiogenic agents.

In this review of the use of etoposide in recurrent malignant gliomas, the activity of this chemotherapeutic agent is demonstrated alone and in a variety of regimens. Etoposide can be given with temozolomide where it yielded four month duration of response [26]. When combined with carboplatin, etoposide provides a median time to progression of 12-16 weeks [27-29]. The ICE regimen demonstrated a median PFS of 13-17 weeks in two studies, while a third heterogeneous group with poor performance status and some who previously failed bevacizumab showed modest median PFS of 8 weeks.

The literature reveals that etoposide regimens have activity in recurrent malignant gliomas. The utilization of etoposide chemotherapy regimens in recurrent malignant gliomas is associated with radiographic total response rates (PR+SD) of 50 – 79%, PFS-6 of 33.3%-35%, and median PFS of 13-17 weeks. The radiographic and survival outcomes from etoposide combined chemotherapy regimens would appear to be superior to monotherapy treatment in the recurrent setting.
[33, 34, 36, 37]

A notable limitation is that many of the trials cited in this review do not give reference to the DNA repair enzyme O(6)-methylguanine-DNA methyltransferase (MGMT)

methylation status of the patients enrolled, which limits inter-trial comparisons. MGMT is known to be a positive prognostic factor with increased survival compared to those with unmethylated MGMT promoter [38]. The treatment effects of MGMT methylation as they pertain to the use of topoisomerase II inhibitors and anti-VEGF therapy are likely minimal as etoposide treated tumors are not affected by MGMT-mediated resistance mechanisms [39].

In addition, the phenomenon of "pseudoresponse" also obscures the evaluation of those patients with favorable radiographic response to treatment [40, 41]. Pseudoresponse is thought to occur due to normalization of cerebral vasculature with subsequent decreased contrast enhancement thus appearing improved despite unchanged nonenhancing tumor seen on MRI T2/FLAIR sequences [41, 42]. The Radiologic Assessment in Neuro-Oncology (RANO) criteria was developed to improve and standardize the evaluation of tumors treated with anti-angiogenic agents thus leading more accurate determinations of true tumor progression than Macdonald criteria assessments [43, 44]. In some of the studies evaluating bevacizumab with etoposide the response is limited by analyses that failed to account for non-enhancing tumor seen on T2-weighted images/FLAIR.

Conclusion

The optimal treatment of malignant gliomas that have failed previous bevacizumab therapy remains controversial. In recurrent malignant gliomas previously treated with anti-angiogenic agents, the use of etoposide with bevacizumab is safe and

clinically active in a selected group of patients. New methods to be able to predict which patients will show benefit from this combination treatment are yet to be developed.

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Tables

Table 1. Recurrent studies containing etoposide combination therapy

Study	Regimen	n=	Tumor Types	Response Rate (%)	Total Response Rate (%)	Median PFS (weeks)	PFS-6 (%)	Median OS (weeks)
Jeremic 1992 [27]	CDDP+VP-16	38	GBM+AA	21	53	14		43.5
Watanabe 2002 [28]	CDDP+VP-16	28	GBM+AA	14/36	57/79			52/132
Franceshci 2004 [29]	CDDP+VP-16	30	GBM+AA	24/ /30	64/ /70	16	33.3	36/ /40
Sanson 1996 [30]	Ifos+CDDP+VP-16	36	GBM+AG	28	53	13		29
Aoki 2010 [31]	Ifos+CDDP+VP-16	42	GBM	25	50	17	35	42.8
Schafer 2011 [32]	Ifos+CDDP+VP-16	13	GBM+AA	0		8	0	20

CBDCA = carboplatin; Ifos = ifosfamide; VP-16 = etoposide

Table 2. Recurrent studies containing etoposide + anti-angiogenic agents

Study	Regimen	n	Tumor Types	Response Rate (%) GBM/AG	Total Response Rate (%)	Median PFS (weeks) GBM/AG	PFS-6 (%) GBM/AG	Median OS (weeks) GBM/AG
Kesari 2007 [33]	VP-16 + Cyclo + Thal + Celecoxib	48	GBM+AG	9	62.5	11	9	42
Reardon 2009 [34]	Bev + VP-16	59	GBM+AG	23/24		18/24	44.4/41	46.4/63.1
Francesconi 2010 [36]	Bev + CBDCA + VP-16	6	GBM	83		19	22	29.9
Reardon 2011 [17]	Bev + VP-16 vs. Bev + TMZ	23	GBM	0	52	8.1		19

AG = AO, AMG; Bev = bevacizumab; CBDCA = carboplatin; Cyclo = cyclophosphamide;

Thal = thalidomide; TMZ = temozolomide; VP-16= etoposide