Original Article

Bevacizumab for Recurrent Glioblastoma Multiforme: A Meta-Analysis

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Key Words
Bevacizumab, glioblastoma, meta-analysis

Abstract
The FDA's approval of bevacizumab for recurrent glioblastoma on May 9, 2009, was based on the significant response rate and clinical benefits seen from randomized phase II studies. Large-scale phase III data are unavailable. In an effort to determine benchmark efficacy parameters for bevacizumab and analyze its dose–response effect, the authors performed a meta-analysis of 15 studies published from 2005 to 2009, involving 548 patients with a median age of 53 years (range, 5–74 years), that used bevacizumab to treat recurrent glioblastoma. Median overall survival was 9.3 months (95% CI, 7.9–10.6 months). The respective 6-month progression-free and 6-month overall survival rates were 45% (95% CI, 34%–57%) and 76% (95% CI, 69%–84%), respectively. Median time to tumor progression was 6.1 months (95% CI, 4.2–8.1 months). The response analysis yielded a 6% complete response (95% CI, 2%–9%), 49% partial response (95% CI, 37%–61%), and 29% stable disease (95% CI, 20%–38%). No difference was seen in bevacizumab dose–response benefit between 5 mg/kg and 10 to 15 mg/kg. The efficacy benchmarks from this meta-analysis did not differ from those of the recently published randomized phase II studies. The lack of a dose–response effect would require confirmation in a prospectively conducted clinical trial. (*JNCCN* 2011;9:403–407)

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Patients with recurrent glioblastoma multiforme have a poor prognosis. Conventional cytotoxic chemotherapies only offer a 6% response rate and a 15% 6-month progression-free survival rate.[1] This poor efficacy was partly a result of arteriovenous shunting of blood around the glioblastoma from elevated interstitial pressure. Therefore, only a minute fraction of oxygen and chemotherapy is delivered to the tumor. In experimental settings, lowering the interstitial pressure by normalizing tumor vasculature improves glioblastoma response to radiation therapy,[2] probably through increasing oxygen delivery and allowing radiation to work better in a normoxic rather than a hypoxic tumor microenvironment.[2,3]

Bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF), has become the standard of care for recurrent glioblastoma. Stark-Vance[4] first used it in 2005 for the empiric treatment of patients with recurrent glioblastoma, which resulted in dramatic improvement of neurologic functions. This observation led to 2 landmark phase II single-arm clinical trials by Vredenburgh et al.[5] and Chen et al.,[6] published independently in 2007, using bevacizumab and irinotecan adopted from a treatment schedule developed for colorectal carcinoma. Vredenburgh et al.[5] used 10 mg/kg of bevacizumab every 2 weeks or 15 mg/kg every 3 weeks, in combination with 340 mg/m^2 of irinotecan for patients taking enzyme-inducing antiepileptic drugs (EIAEDs) or 125 mg/m^2 of irinotecan for those not taking antiepileptic drugs or on non-EIAEDs. They reported a response rate of 57% and 6-month progression-free survival rate of 46%. Similar favorable results were noted by Chen et al.,[6] with a response rate of 47% and 6-month progression-free survival rate of 65%. Later, in an effort to gain the FDA's approval of bevacizumab for recurrent glioblastoma, 2 randomized phase II studies compared the efficacy of bevacizumab alone versus either bevacizumab plus sequential irinotecan (06-C-0064E trial[7]) or

bevacizumab plus concurrent irinotecan (AVF3708 trial[8]). In the 06-C-0064E trial, bevacizumab used at 10 mg/kg every 2 weeks showed a response rate of 35% and 6-month progression-free survival rate of 29%.[7] In the AVF3708 trial, bevacizumab used at 10 mg/kg every 2 weeks showed a response rate of 28.2% and 6-month progression-free survival rate of 42.6% when used alone, and 37.8% and 50.3%, respectively, when combined with irinotecan.[8] But overall survival was not prolonged in either trial. Therefore, these data suggest that the predominant anti-glioblastoma effect comes from bevacizumab alone. Furthermore, based on the significant response rate and clinical benefit seen in these trials, the FDA granted accelerated approval on May 9, 2009, for bevacizumab to be used as a single-agent treatment for recurrent glioblastoma.

The optimal bevacizumab schedule has not been determined. Published clinical trials used bevacizumab at doses of 5 mg/kg every 2 weeks, 10 mg/kg every 2 weeks, 10 mg/kg every 4 weeks, and 15 mg/kg every 3 weeks, resulting in a respective dose intensity of 30 mg/kg, 60 mg/kg, 30 mg/kg, and 60 mg/kg, respectively, within a 12-week period. This heterogeneous dose intensity may result in slightly different rates of response, 6-month progression-free survival, and overall survival. Therefore, this meta-analysis was performed to determine benchmark parameters for bevacizumab's benefit on recurrent glioblastomas and to analyze its dose–response effect.

Methods

Comprehensive electronic searches of published studies (abstracts excluded) using bevacizumab for malignant gliomas were performed using MEDLINE Plus/OVID from the Countway Library at Harvard Medical School. Only reports on treatment of recurrent glioblastoma patients were analyzed and the following data were collected: overall survival, 6-month overall survival, 6-month progression-free survival, time to tumor progression, and response. Linear regression analysis was used to determine the median overall survival, 6-month overall survival, 6-month progression-free survival, time to progression, and response. Response was further subcategorized into complete response, partial response, and stable disease. Wilcoxon rank sum test was used to compare dose–response effect on overall survival, 6-month overall survival, 6-month progression-free survival, and time to progression. Significance level was defined at $P \leq .05$.

Results

From 2005 to 2009, 18 publications reported on bevacizumab-based treatment in 621 patients with malignant gliomas. Of these, 3 reports were excluded because 2 were on anaplastic gliomas and 1 used bevacizumab at both initial diagnosis and recurrence. Thus, the final data set consisted of 548 patients with glioblastoma from 15 reports (Table 1). The median age was 53 years (range, 5–74 years). Twelve reports documented the use of irinotecan in combination with bevacizumab, whereas 2 used bevacizumab alone and 1 combined stereotactic radiosurgery with bevacizumab. Other cytotoxic chemotherapies included carboplatin, carmustine, etoposide, lomustine, and liposomal doxorubicin. The median overall survival was 9.3 months (95% CI, 7.9–10.6 months). The 6-month progression-free and 6-month overall survival rates were 45% (95% CI, 34%–57%) and 76% (95% CI, 69%–84%), respectively. Median time to progression was 6.1 months (95% CI, 4.2–8.1 months). Among the patients, 6% experienced complete response (95% CI, 2%–9%), 49% partial response (95% CI, 37%–61%), and 29% stable disease (95% CI, 20%–38%).

To determine whether a dose–response occurs with bevacizumab, the authors extracted information on dosing from published data. Only one publication documented the use of 15-mg/kg dosing in 12 patients. Because of this small number of patients, the 10- and 15-mg/kg dosing cohorts were combined (n = 462) before being compared with the 5-mg/kg dosing cohort (n = 86) for evidence of a dose–response. Bevacizumab at 10 to 15 mg/kg had no dose–response benefit over 5 mg/kg with respect to 6-month progression-free survival ($P = .223$), 6-month overall survival ($P = .145$), complete response ($P = .997$), partial response ($P = .639$), and stable disease ($P = .428$) (Table 2).

Discussion

The dose of bevacizumab currently in use for recurrent glioblastoma was chosen empirically. No phase I study was performed in this patient population to

Table 1 List of Publications on Bevacizumab Treatment for Recurrent Glioblastoma

Author	Number of Patients	Median Age in Years (min, max)	Bevacizumab Dose (mg/kg)	Combined With	Treatment Cycle (wk)	CR (%)	PR (%)	SD (%)	TTP (mo)	PFS-6 (%)	OS-6 (%)
Ali et al.[16]	13	53 (22,76)	5,10	Irinotecan	2	0	85	15	5.5	N/A	N/A
Almubarak et al.[17]	1	56 (N/A, N/A)	10	Liposomal doxorubicin	2	0	100	0	8	100	100
Ananthnarayan et al.[18]	15	61 (39, 90)	5	None, irinotecan, carboplatin, etoposide, lomustine	2	7	67	20	2.4	N/A	N/A
Bokstein et al.[19]	17	56 (38, 74)	5	Irinotecan	2	11	37	11	4.7	25	55
Chen et al.[6]	17	58 (26, 78)	10	Irinotecan	2	0	19	48	2.4	N/A	65
Friedman et al.[8]	85	54 (23, 78)	10	None	2	1	27	72	N/A	43	74
	82	54 (23, 78)	10	Irinotecan	2	2	35	63	N/A	50	75
Gutin et al.[20]	20	56 (30, 80)	10	Radiosurgery	2	20	32	48	N/A	65	92
Kang et al.[21]	12	46 (5, 69)	10	Irinotecan	4	0	44	41	N/A	17	75
Kreisl et al.[7]	48	53 (21, 69)	10	None	2	2	33	20	N/A	29	57
Narayana et al.[22]	37	56 (15, 77)	10	Irinotecan, carboplatin	2	13	60	21	N/A	44	74
Nghiemphu et al.[23]	44	55 (26, 90)	5	Irinotecan, carboplatin, etoposide, lomustine	2	N/A	N/A	N/A	11	41	70
Norden et al.[24]	33	50 (23, 71)	5,10	Irinotecan, carboplatin, carmustine	2	2	32	30	4.8	42	64
Poulsen et al.[25]	52	46 (26, 67)	10	Irinotecan	2	10	15	40	N/A	40	54
Vredenburgh et al.[5]	35	48 (18, 66)	10,15	Irinotecan	2,3	N/A	57	43	4.6	46	77
Zuniga et al.[26]	37	53 (20, 74)	10	Irinotecan	2	5	62	16	N/A	64	78

Abbreviations: CR, complete response; NA, not available; OS-6, 6-month overall survial; PFS-6, 6-month progression-free survival; PR, partial response; SD, stable disease; TTP, time to progression.

evaluate the toxicity and optimal efficacy of escalating doses of bevacizumab. Stark-Vance[4] initially treated patients with 5 mg/kg of bevacizumab in combination with irinotecan and saw symptomatic improvement. The subsequent bevacizumab dosing schedules for glioblastoma were 10 mg/kg every 2 weeks and 15 mg/kg every 3 weeks, and the combination with irinotecan was adopted from the treatment schedule developed for colorectal carcinoma. As a result, the dose that provides optimal control of recurrent glioblastoma remains unknown. This meta-analysis is limited by the lack of uniformity in reporting benchmark efficacy data by investigators. The 6-month progression-free and 6-month overall survival rates, which are generally accepted clinical trial end points for recurrent glioblastoma, were not reported in 13% of the trials. Data were also missing on response rate and time to progression in 7% and 40% of the trials, respectively. In addition, 8 studies also reported on anaplastic gliomas, which were included in this meta-analysis only when glioblastoma histology was in the majority. The rationale for including these 8 studies is based on the similar and poor 6-month progression-free and progression-free survival data on glioblastoma and anaplastic gliomas treated with salvage cytotoxic chemotherapies.[1] Although the original source data were not obtained from the individual investigators, findings on the overall benchmark measure of efficacy for the 10- to 15-mg/kg dose, such as response, 6-month progression-free survival, and 6-month overall survival rates, were similar to those seen in the 2 randomized phase II studies that led to FDA approval of bevacizumab.[7,8]

Table 2 Bevacizumab at Doses of 5 mg/kg Versus 10–15 mg/kg

	Number of Patients	CR	PR	SD	PFS-6	OS-6
Dose (mg/kg)						
5	86	7%	56%	16%	36%	66%
10–15	462	6%	41%	37%	34%	74%
P		.997	.639	.428	.223	.145
All patients	548	6%	49%	29%	45%	76%

Abbreviations: CR, complete response; OS-6, 6-month overall survival; PFS-6, 6-month progression-free survival; PR, partial response; SD, stable disease.

This meta-analysis did not find bevacizumab to have a dose–response effect against recurrent glioblastoma, perhaps because of its mechanism of action. Bevacizumab neutralizes VEGF from the circulation, and probably from the extracellular space within the tumor. Because each VEGF can interact with multiple VEGF receptors (VEGFRs), removal of each ligand can lead to an exponential decrease in receptor signaling within endothelial cells. Through depleting VEGF below the required threshold level, the amount of VEGF available would be insufficient to trigger signal transduction via its receptors for angiogenesis within the glioblastoma, and therefore tumor vasculature regresses. This potential threshold effect also indicates that bevacizumab may not need to completely neutralize all VEGF ligands to produce clinical benefit. In contrast, VEGFR tyrosine kinase inhibitor (TKI) probably operates in a linear fashion, and antiangiogenesis may occur only when nearly all of the receptors are individually blocked. This concept is supported by recent data from De Groot et al.[9] showing that bevacizumab blocked the migration of proangiogenic, VEGFR1-expressing $CD11b^+$ myeloid cells into orthotopically implanted glioblastoma in mice and prolonged their survival. But sunitinib, a VEGFR TKI, did not have this benefit.[9] Furthermore, when glioblastoma patients failed VEGFR TKIs, bevacizumab treatment still offered benefit, with a response rate of 21% and 6-month progression-free survival rate of 12.5%.[10] Therefore, anti-VEGF therapy may have a greater therapeutic index than VEGFR inhibition.

It is unclear whether a high or low dose of bevacizumab would produce a corresponding faster or slower clinical benefit, respectively. For example, bevacizumab at 10 or 15 mg/kg may produce the maximal clinical benefit sooner than at 5 mg/kg. Therefore, patients with severe cerebral edema and impending cerebral herniation may benefit from a higher dose of bevacizumab (10–15 mg/kg), as long as no evidence of cerebral hemorrhage is seen. However, the effects of these different doses require further investigation in a prospectively conducted clinical trial.

Bevacizumab also has an inconsistent dose–response relationship in other malignancies. In metastatic colorectal carcinoma, patients treated with bevacizumab at 5 mg/kg plus 5-fluorouracil (5-FU) and leucovorin (LV) had a slightly higher median survival than those treated with bevacizumab at 10 mg/kg plus 5-FU/LV. However, the difference between these groups was not statistically significant.[11] In metastatic non–small cell lung cancer, the benefit of bevacizumab at 15 mg/kg every 3 weeks was only slightly higher than at a lower dose of 7.5 mg/kg when both drugs were combined with carboplatin and paclitaxel.[12] The higher bevacizumab dose only offered an improvement in median time to progression but not response rate or overall survival.[12] In metastatic renal cell carcinoma, no difference was seen between bevacizumab doses of 3 and 10 mg/kg with respect to response rate, time to progression, and overall survival.[13] Likewise, in metastatic breast carcinoma, no difference was seen in response rates for doses of 3 mg/kg, 10 mg/kg, and 20 mg/kg.[14] Taken together, bevacizumab in patients with systemic malignancies has shown no difference in efficacy at doses less than 10 mg/kg and those 10 mg/kg or greater.

Using a lower dose of bevacizumab may result in substantial savings. At a cost of $9000 per dose[15] and a 6-month progression-free survival rate of 30% to 50% for bevacizumab-based treatment,[5–8] the average patient with recurrent glioblastoma would receive approximately 13 doses of bevacizumab over 6 months, at an aggregate cost of $117,000. If the dosing could be lowered to 5 mg/kg, bevacizumab use could be reduced by half, resulting in a substantial

savings of $58,500. However, the cost-effectiveness of 5 versus 10 mg/kg of bevacizumab in patients with glioblastoma must be prospectively analyzed.

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