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Deferred use of bevacizumab for recurrent glioblastoma is not associated with diminished efficacy

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Background. The optimal timing to initiate bevacizumab (BV) therapy for recurrent glioblastoma (GBM) is currently unclear. To address this issue, we examined progression-free survival (PFS) and survival time (ST) in a large retrospective cohort of GBM patients treated with BV at different recurrences.

Methods. We identified 468 primary GBM patients who underwent biopsy or surgery followed by radiation therapy and temozolomide (RT/TMZ), and then received BV. PFS and ST were compared between patients stratified by the recurrence that BV was initiated (upfront, first recurrence, second recurrence, or 3+ recurrences). We also examined the effect on PFS and ST of the addition of chemotherapy to BV. In a larger cohort of GBM patients, we determined overall treatment continuation rates at each recurrence and identified variables predictive of inability to continue treatment.

Results. BV PFS was similar for all 3 recurrence groups (median, 4.1 months). There were no differences in BV ST (median, 9.8 months). The addition of chemotherapy to BV improved PFS but not ST. Analysis of treatment continuation rates indicated that the number of patients unable to undergo further treatments is modest, and that patients unable to tolerate BV delay can be identified by age $\geq$60 years and low extent of resection.

Conclusions. Deferred use of bevacizumab is not associated with diminished efficacy. Analysis of treatment continuation rates identified patients who may be unable to delay BV therapy. Our findings suggest that there is a fixed survival after BV initiation and that delayed BV treatment is preferable for most patients.

Keywords: bevacizumab, recurrent glioblastoma, retrospective study, treatment continuation.

Glioblastoma (GBM) is the most common malignant primary brain tumor, and prognosis remains poor despite aggressive treatment. First-line therapy with surgery, radiation, and concurrent temozolomide (TMZ), followed by adjuvant TMZ, is the standard of care for GBM.[1] Despite treatment with chemoradiation, progression inevitably occurs. GBMs are characterized by necrosis, endothelial proliferation, and vascular endothelial growth factor (VEGF) production. VEGF stimulates neovascularization, leading to tumor growth. Bevacizumab (BV) is an anti-VEGF monoclonal antibody used for treating recurrent GBM, which leads to vascular pruning, decreased edema, and improvement of contrast enhancement on imaging. A number of treatment options including BV are available at progression, but the optimal timing and order of administration of therapy for recurrent disease is unknown. Based on 2 phase II trials, BV was FDA-approved as monotherapy for recurrent GBM in 2009 through the accelerated approval

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process and has been the hallmark of care in the United States since its approval.[2,3] However, it was not approved in Europe for treating recurrent GBM at that time due to lack of randomized phase III data. In the United States, virtually all GBM patients will receive BV at some point during their treatment course.

GBM is an aggressive disease, with a median survival of only 14.6 months.[1] In some academic series in the post-BV era, median overall survival (OS) approaches 16 to 20 months, although the reasons for this are unidentified.[4–7] One possibility is the emergence of BV treatment, although there is no definitive evidence to date that BV extends OS. Despite the widespread use of BV, the optimal time for starting BV therapy (whether at early or later recurrence) remains unclear. Two phase III clinical trials evaluating BV as first-line therapy have now been completed.[8–10] The results indicate that OS for upfront use of BV is not superior to BV at recurrence, which therefore reinforces the need to carefully examine optimal timing for BV administration. More significantly, it has become all too clear that prognosis following failure of BV therapy remains poor, with no additional agents demonstrating improved survival.[11–14]

Practice styles regarding the use of BV vary widely, including when to initiate treatment and if concurrent chemotherapy should be used. A number of patients also participate in clinical trials or undergo other treatments before receiving BV at a later recurrence. The efficacy and survival rates of delayed BV therapy are unknown when it is deferred while other treatment options are being pursued. To address these issues, we performed a retrospective study of participants treated with BV at our institutions to determine how these factors impact survival. To complement these data, we also examined rates of overall treatment continuation following recurrence, since some patients may not survive or maintain adequate functional status to receive subsequent recurrent therapies and therefore may not benefit from BV if it is delayed.

Materials and Methods

Study Population

Based on an electronic database query of adult primary GBM patients receiving upfront RT and TMZ (gliosarcoma was excluded), we identified a cohort of 468 primary GBM patients treated with BV at University of California Los Angeles (UCLA) or Kaiser Permanente Los Angeles (KPLA). These included 15 patients with known IDH1/2 mutations, who were likely to have clinically "silent" secondary GBMs but whose initial diagnosis was GBM and not a lower-grade glioma. Patients initiated BV for glioblastoma between 2005 and 2012 (29 participated in the BRAIN study and 69 in the NCT01013285 trial). For the 29 participants in the BRAIN trial, 25 received BV at first recurrence and 4 at second recurrence.[5,15] Participants were stratified by the recurrence in which they received BV and were grouped into upfront, first, second, or third or more(3+) recurrences. Of the 388 participants who received BV at recurrence, 121 received BV monotherapy, and 267 were treated with BV plus concurrent chemotherapy (BV+). A summary of patient characteristics is provided in Table 1. All participants underwent biopsy or surgery with a confirmed tissue diagnosis of GBM. The pathology slides for 306 of 468 participants were reviewed at our institutions. For the remaining 162 participants, the outside pathology report was used to confirm the diagnosis of GBM. All patients were included if they had subsequent follow-up at our institutions and for whom there was sufficient information to generate radiation therapy (RT)/TMZ progression-free survival (PFS), BV PFS, survival after bevacizumab failure (Post-BVS), and BV survival time (ST) intervals. All participants provided informed consent in a UCLA/KPLA IRB-approved database study to collect clinical, pathological, and imaging information to be used for future retrospective studies. Follow-up of all participants was continued through February 2013.

Survival Intervals

Dates of progression were determined at the time of imaging by the treating clinician, based on modified Levin criteria considering both contrast-enhancing and noncontrast-enhancing tumor, as previously utilized.[5,16] Imaging progression was based on changes in the T1 with contrast or T2 or appearance of any new lesion, while taking into account changes in corticosteroid dose, and was a close approximation to the current RANO criteria. Because some of the data predate RANO, those criteria were not used for this study. For PFS, participants were censored at the date of the last stable imaging; for ST, participants were censored at the date of the last clinical contact. We calculated the following survival periods for each participant: RT/TMZ PFS, BV PFS, post-BVS, and BV ST. The RT/TMZ PFS was calculated by the date of initial surgery to first progression. The BV PFS was calculated between the date of the first BV and the date of progression on BV. The post-BVS was the date of progression on BV until the date of death or censor date. Finally, the BV ST was calculated between the date of BV initiation to the date of death or censor date (Fig. 1).

Treatment Continuation Rates

We sought to determine the fraction of all GBM participants who were able to continue treatment at each recurrence, irrespective of BV use, to determine who might be candidates for delayed BV therapy. We evaluated a second cohort of participants in our database who were diagnosed with primary glioblastoma and treated upfront with RT/TMZ, and we used this cohort of 1342 individuals to determine treatment continuation rates. The 468 patients already described above were included in the cohort of 1342 participants. All subsequent options at recurrence were included including death, hospice, clinical trials, BV, or other chemotherapy. We calculated the fraction of participants who would not receive additional treatment at each subsequent recurrence. We identified all participants who (A) progressed by death or (B) progressed but received no further therapy (ie, hospice) at each recurrence. Our treatment continuation rate was calculated as $1-[(A+B)/(A+B+Y)]$, where Y was the number of paticipants who progressed and received any additional treatment.

Data Analysis

The Student *t* test, chi-square test, and Kruskal-Wallis test were used to compare differences in participant characteristics. Survival analysis used SAS software, and estimated Kaplan-Meier curves were compared via the log-rank test. Differences were defined as statistically significant if $P < .05$. Univariate and multivariate survival analyses were performed using the Cox proportional hazards regression model. Accuracy was assessed using

Table 1. Patient characteristics by the recurrence in which bevacizumab was initiated

Characteristics	Recurrence When Bevacizumab Initiated					*P* value
	Upfront *n* ¼ 80 (%)	First *n* ¼ 264 (%)	Second *n* ¼ 88 (%)	3+ *n* ¼ 36 (%)	Total *n* ¼ 468 (%)	
Sex						NS
Female	34 (42.5)	91 (34.5)	41 (46.6)	10 (27.8)	176 (37.6)	
Male	46 (57.2)	173 (65.5)	47 (53.4)	26 (72.2)	292 (62.4)	
Age at surgery						NS
Median	56.5	57.5	56.6	49.2	56.6	
IQR	50.4–63.2	49.3–64.0	49.9–66.5	34.0–58.6	49.0–63.9	
Age at BV						*.006
Median	56.6	58.3	58	51.3	57.6	
IQR	50.5–63.2	50.6–64.7	51.2–67.7	38.3–62.0	50.0–64.8	
KPS at BV						NS
80–100	71 (88.8)	201 (76.5)	64 (72.7)	27 (75.0)	363 (77.7)	
≤70	9 (11.2)	62 (23.5)	24 (27.3)	9 (25.0)	104 (22.3)	
BV treatment						NS
Combined		181 (68.6)	61 (69.3)	25 (69.4)	267 (68.8)	
Monotherapy		83 (31.3)	27 (30.7)	11 (30.6)	121 (31.2)	
MGMT						NS
Methylated	30 (38.5)	36 (34.6)	12 (37.5)	7 (31.8)	85 (36.0)	
Unmethylated	48 (61.5)	68 (65.4)	20 (62.5)	15 (68.2)	151 (64.0)	
[not done]	[2]	[160]	[56]	[14]	[232]	
IDH1						**.029
Mutant	5 (6.4)	3 (2.5)	3 (7.7)	4 (16.7)	15 (5.8)	
Wild-type	73 (93.6)	115 (97.5)	36 (92.3)	20 (93.3)	244 (94.2)	
[not done]	[2]	[146]	[49]	[12]	[209]	

*t test.
**Chi-square test.
Abbreviations: BV, bevacizumab, IQR, interquartile range; KPS, Karnofsky performance status.

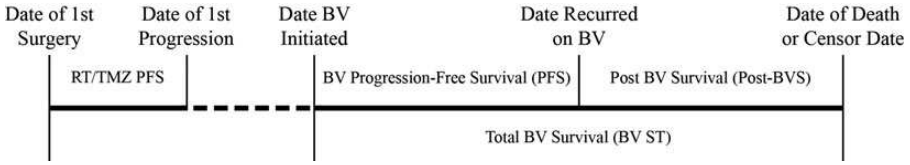

Fig. 1. Survival intervals.

the bootstrap method by estimating the distribution of median PFS and the differences of median PFS values. We used random resampling with replacement to get 1000 samples. Classification and regression tree (CART) analysis (excluding patients with missing covariates) and logistic regression were used to determine factors associated with treatment discontinuation. Among the 1342 participants who were newly diagnosed with GBM and received RT/TMZ, only 24 had missing covariates. Therefore, neither imputation nor surrogate split was used for CART and logistic regression analyses. For these analyses, there were no missing data for the dependent variable and very few missing for the covariates. The covariates included in the CART and logistic regression analyses were age, sex, KPS, extent of resection, and MGMT methylation status. Additional methods for the CART and logistic regression analyses are provided in the supplement.

Molecular Markers

In the cohort of 468 BV participants, MGMT promoter methylation status was available for 158 of the 388 participants treated with BV at recurrence and 30 of 80 participants who received BV upfront.[5,17] IDH mutation status was available for 259 of the 468 participants. Fifteen participants harbored IDH mutations, and 244 were wild-type (Table 1). Additional information is provided in the supplement.

Results

Participant Characteristics

As described in the Methods section, we derived a cohort of 468 participants who received BV between 2005 and 2012. Eighty

participants received BV as upfront therapy along with standard RT/TMZ. Two hundred sixty-four participants were treated with BV at first recurrence, 88 at second recurrence, and 36 at the 3+ recurrence. The initial characteristics were similar among the groups except for younger age at BV initiation (*t* test, *P* ¼ .006) in the 3+ recurrence group and a greater frequency of IDH mutation (chi-square test, *P* ¼ .029, Table 1).

BV PFS Remains Unchanged When Used at Later Recurrences

We sought to determine if there were differences in BV efficacy when BV was delayed to later recurrences. We stratified participants receiving BV therapy by recurrence and compared PFS among the cohorts. Those who received BV at second or greater recurrence were treated with other salvage chemotherapies or clinical trial agents prior to the recurrence in which BV was started. The median BV PFS for the first, second, and 3+ groups was 4.1 months (95% CI, 3.7mo–4.5mo), 4.2 months (95% CI, 3.2mo–5.3mo), and 3.4 months (95% CI, 1.9mo–5.0mo), respectively, and was not significantly different (log rank test *P* ¼ .0895, Fig. 2). A Cox proportional hazards model with age, sex, KPS, number of prior recurrences, and MGMT status as covariates also showed no differences in hazard ratio (HR), indicating that BV PFS was not diminished by initiating therapy at later recurrences (Table 2).

To assess the accuracy of our findings, we estimated the distribution of the median PFS between the first and second recurrence groups and the difference of the median PFS using the bootstrap method. We used random resampling with replacement to get 1000 samples; each sample had 264 participants who received BV at the first recurrence and 88 who received BV at the second recurrence. There was no significant difference between estimated median PFS values (*P* ¼ .1360).

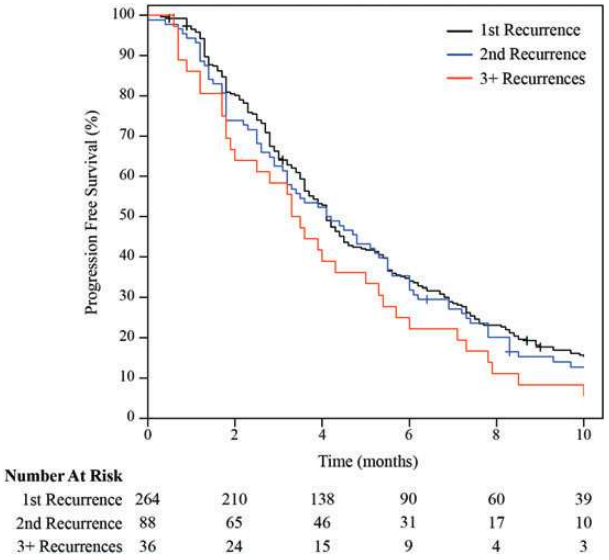

Fig. 2. Bevacizumab progression-free survival (BV PFS) is independent of recurrence. BV PFS was stratified by the recurrence that therapy was initiated and was maintained when therapy was initiated at later recurrences.

There were only 10 known participants across all 3 recurrence cohorts with IDH1/2 mutations, and IDH status was not included in multivariate analyses. However, when the BV PFS for the 10 IDH1/2 mutations was compared with the 171 participants with wild-type IDH1/2, there was no clear improvement in PFS (log rank 0.727, Supplementary Fig. S1). MGMT methylation status determined at initial surgery was included in the multivariate analyses and was associated with a longer BV PFS (Table 2) but not a longer BV ST (Table 3).

Delay of BV Does Not Affect BV ST or Post-BVS

Next, we evaluated the effect of the same variables on ST from BV initiation. Figure 3 compares the BV ST for each cohort. The median BV ST for the first, second, and 3+ groups was 8.4 months (95% CI, 8.0mo–9.8mo), 9.3 months (95% CI, 7.2mo–10.7mo), and 6.4 months (95% CI, 5.1mo–9.4mo), respectively. There were no differences in BV ST when stratified by recurrence (log rank test *P* ¼ .7616). A Cox proportional hazards model did not show any differences between the cohorts (Table 3). This indicates that patients have "fixed" survival from when BV is initiated and suggests that delaying BV may be beneficial.

To confirm these results, we also evaluated the survival post-BV failure among participants who went on to receive additional treatment after BV failure. Sixty of the 468 participants did not have a post-BVS period due to death and were excluded. In addition to the 3 recurrence cohorts, the post-BVS for a cohort of 80 participants who received BV in the upfront setting was also compared with the recurrence cohorts. There were no differences in post-BVS among the 4 groups (log rank test *P* ¼ .576, Fig. 4). Although the BV PFS was different for the group of upfront BV participants, the post-BVS was comparable to participants who initiated BV at recurrence. Multivariate analysis did not show any differences among the 4 groups (Supplementary Table S1). For participants able to continue to the next treatment

Table 2. Multivariate analysis of progression-free survival by recurrence in which bevacizumab was initiated

Factors	HR (95% CI)	*P* value
Recurrence		
1st	1.0 (ref)	
2nd	1.11 (0.86–1.42)	.4221
3+	1.33 (0.93–1.90)	.1221
Age	1.00 (0.99–1.01)	.7907
Sex		
Male vs female	1.22 (0.98–1.52)	.0718
KPS		
≤70 vs 80–100	1.22 (0.96–1.56)	.107
MGMT		
Unmethylated	1.0 (ref)	
Methylated	0.60 (0.43–0.85)	.0036
Not done	0.74 (0.58–0.94)	.0145
BV treatment		
BV only vs BV+	1.27 (1.01–1.60)	.0416

Abbreviations: BV, bevacizumab; BV+, bevacizumab plus concurrent chemotherapy; KPS, Karnofsky performance status.

Table 3. Multivariate analysis of survival time by recurrence in which bevacizumab was initiated

Factors	HR (95% CI)	*P* value
Recurrence		
1st	1.0 (ref)	
2nd	1.05 (0.81–1.37)	.6962
3+	1.11 (0.76–1.62)	.5943
Age	1.02 (1.01–1.02)	.0007
Sex		
Male vs female	1.37 (1.09–1.72)	.0073
KPS		
≤70 vs 80–100	1.34 (1.04–1.73)	.0251
MGMT		
Unmethylated	1.0 (ref)	
Methylated	0.73 (0.52–1.04)	.0837
Not done	0.96 (0.74–1.23)	.7395
BV treatment		
BV only vs BV+	0.98 (0.77–1.24)	.8682

Abbreviations: BV, bevacizumab; BV+, bevacizumab plus concurrent chemotherapy, KPS, Karnofsky performance status.

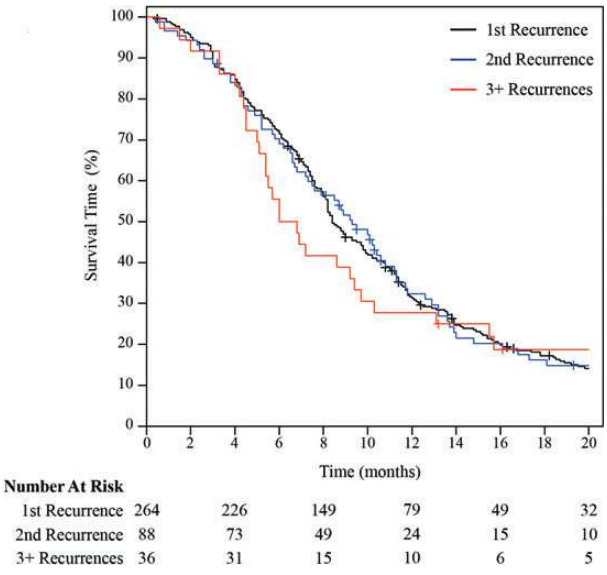

Fig. 3. Bevacizumab survival time (BV ST) is independent of recurrence. BV ST was stratified by the recurrence at which therapy was initiated and was unchanged when therapy was initiated at later recurrences.

after BV failure, there was no difference in post-BVS, indicating that survival following BV failure is constant and independent of prior therapy.

Next, we compared the survival between participants who received BV after progression on BV (either as continued BV monotherapy or BV with additional chemotherapy) with those who did not receive any further BV after progression. There was no difference in survival between participants who continued on a BV-based regimen when compared with those who did not

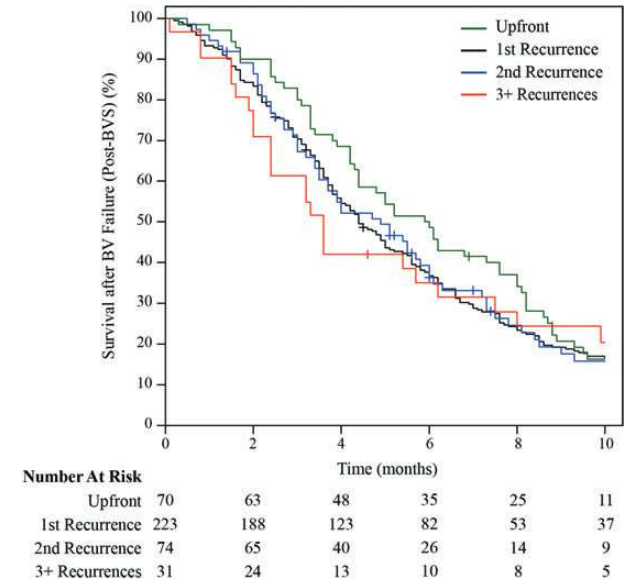

Fig. 4. Survival after bevacizumab (BV) failure is independent of recurrence. Survival after bevacizumab failure (Post-BVS) was stratified by the recurrence that therapy was initiated and was fixed whether therapy was initiated at later recurrences.

receive any further BV (HR, 1.13; 95%, CI 0.85–1.51; $P < .394$; Supplementary Table S1).

Addition of Chemotherapy to BV Improves PFS But Not ST

Although BV is approved for monotherapy for recurrent GBM, there have been multiple attempts to add additional cytotoxic chemotherapy in order to improve outcomes.[13,15,18–20] To determine if the addition of chemotherapy to BV impacted PFS, we stratified all of the 388 recurrent BV participants into those who initially received BV monotherapy and those who received BV plus concurrent cytotoxic chemotherapy (BV+). The most common chemotherapies used along with BV were irinotecan and lomustine (Supplementary Table S2). One-hundred twenty-one patients received BV monotherapy, and 267 patients were treated with BV+. The median PFS for the BV monotherapy group across all recurrences was 3.6 months (95% CI, 3.1mo–4.1mo), and the median PFS for BV+ was 4.3 months (95% CI, 4.0mo–5.3mo). There was a trend to significance in PFS (log rank test P ¼ .103), which was significant on multivariate analysis (Table 2; HR 1.27; 95% CI, 1.01–1.60). However, there was no difference in ST between the BV and BV+ cohorts by multivariate analysis (HR 0.98; 95% CI, 0.77–1.24; Fig. 5 and Table 3). BV PFS but not ST was improved by concurrent cytotoxic chemotherapy at BV initiation.

Identifying Participants Able to Delay BV Therapy

Although our results suggested that delayed BV therapy does not decrease its efficacy, we recognized that a subset of participants at any recurrence may not be able to receive BV at a subsequent recurrence due to death or poor function, and we hypothesized that risk factors for such patients can be identified. Therefore, to identify patients who may not tolerate delayed BV initiation,

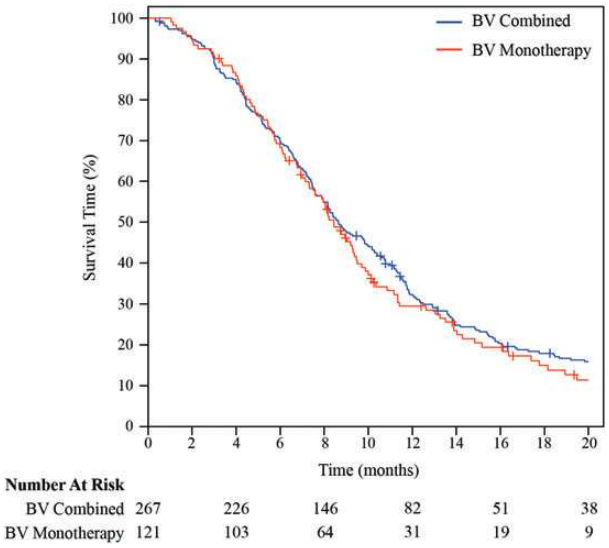

Fig. 5. Addition of chemotherapy to bevacizumab (BV) did not improve survival time. The survival time for BV monotherapy was compared with BV plus the addition of traditional cytotoxic chemotherapy (BV+) and was unchanged when additional cytotoxic chemotherapy was used.

we determined the likelihood of receiving another treatment after a recurrence. We evaluated 1342 participants at our institution who were initially diagnosed with pathology-confirmed primary GBM and received upfront RT/TMZ. We determined the number of participants who experienced recurrence and were able to receive additional treatment for that recurrence. The overall treatment continuation rate was 85.7% between upfront therapy and the first recurrence, 79.9% between the first and second recurrences, and 74.8% between the second and third recurrences. We found that the overall treatment continuation rate was high following a recurrence. Next, we performed CART and logistic regression analysis to determine factors predictive of inability to continue treatment at recurrence. Both logistic regression and CART analysis demonstrated that age ≥60 years and biopsy only were predictive of being unable to continue from upfront treatment to first recurrence, and age ≥ 60 years was predictive of being unable to continue from first to second recurrence (Table 4).

Table 4. Predictors of inability to continue treatment

	% Unable to Continue Treatment	OR (95% CI)	*P* value
Between new and first recurrences	14.3		
Predictive factors			
Age			
≥60y vs <60y		4.23 (2.90–6.15)	<.0001
Extent of resection			
Biopsy		1.0 (ref)	
STR		0.40 (0.26–0.60)	<.0001
GTR		0.22 (0.14–0.36)	<.0001
Between 1st and 2nd recurrences	20.1		
Predictive factors			
Age			
≥60y vs <60y		1.92 (1.33–2.79)	.0006
Extent of resection			
Biopsy/STR		1.0 (ref)	
GTR		0.69 (0.47–1.02)	.0636

Abbreviations: GTR, gross total resection; STR, subtotal resection.

Discussion

Since FDA approval in 2009, BV has become commonly used for recurrent GBM, but the optimal timing of its use is still unknown. We performed a retrospective analysis of 468 glioblastoma participants treated with BV at different recurrences including 80 who were treated upfront. We found that BV PFS was similar whether given at early or late recurrences (upfront participants were not included in this analysis). In addition, we showed that BV ST was also similar at each recurrence, suggesting that BV ST is fixed whether given early or late. While initial therapy with BV is often helpful in improving both imaging features of the tumor and quality of life measures, our data suggest that most, if not all, patients progress after initiation of BV with lack of response to additional treatment and have a predictable remaining survival.[21–23] Furthermore, the survival after BV failure was similar across all recurrences, including participants treated with BV upfront.

The median BV PFS and BV ST reported in this study are similar to numbers reported in prospective clinical trials, suggesting that despite the biases of a retrospective review, the "fixed" response to BV reported here has been observed in prospective randomized trials as well. In the AVF3708g (BRAIN) phase II trial of BV for recurrent glioblastoma, participants at first or second recurrence were randomized to BV alone or BV plus irinotecan.[15] The median ST in the BV group was 9.1 months at first recurrence and 9.2 months at second recurrence. In the BV-plus-irinotecan group, the median ST was 8.7 months at first recurrence and 7.0 months at second recurrence. These numbers are similar to the median BV ST in this study of 8.4 months for first recurrence and 9.3 months for second recurrence. In the Phase II NCI 06-C-0064E trial, heavily pretreated participants were also treated with BV or BV plus irinotecan.[12] The median ST in that study was 7.2 months. The median BV PFS was 3.73 months, which was again comparable to the median BV PFS across all groups in this study (4.1 months).

Currently there is no consensus on the efficacy of combining cytotoxic therapy with BV, and practice patterns vary considerably. We evaluated the effect of adding chemotherapy to BV. We found that combining BV with chemotherapy was associated with a small improvement in PFS (0.7 months) but did not translate into an improved ST. While the BRAIN trial did not formally compare BV to BV plus irinotecan, there was a trend for improved PFS in the irinotecan arm that did not translate to an improved OS (median PFS 4.2 months for BV and 5.6 months for BV+ irinotecan; median OS 9.2 months for BV and 8.7 months for BVplus irinotecan), supporting our conclusion that there were no

differences in ST between BV monotherapy and BV+. Although we found a modest improvement in PFS in our analysis, adding chemotherapy to BV increases the cost of therapy as well as the possibilities for additional toxicities and decreased quality of life without a clear benefit in ST.[19,24]

As with all retrospective studies, there are a number of inherent limitations. While many of the participant demographics were similar, there were some differences among the cohorts. Most notably, there was a younger median age at initiation of BV therapy and a greater frequency of known *IDH1/2* mutations in the 3+ recurrence group. As this was a retrospective study, assignment to the treatment groups was determined by the treating clinician. There is also an inherent selection bias for the participants who survived to the second or 3+ recurrence cohorts that favors a group of participants who continued to do well despite multiple recurrences.

One might argue that the BV PFS and ST for the 3+ group may trend lower than the first or second recurrence group, even if not statistically significant. While this group had the youngest participants and highest percentage of those with *IDH1/2* mutation, interestingly it also had the lowest percentage of MGMT methylation (31.8%). However, despite pretreatment differences among the BV cohorts such as age and *IDH1/2* mutation status, the fixed effect of BV on PFS and ST was remarkably the same, suggesting that pretreatment characteristics do not affect survival after BV administration. The effect of BV on PFS and ST needs to be evaluated in a randomized, prospective fashion.

Our results indicate that BV efficacy is not diminished at later recurrences and suggests that delayed use of BV may be preferable. However, we recognize that some patients are unable to receive further recurrent treatments due to death or rapid clinical deterioration. In these patients, delayed BV treatment may represent withholding a treatment that may benefit them. To identify patients who may not be able to delay BV therapy, we determined the percentage of patients that were unable to continue treatment at recurrence. We found that most participants were able to receive treatment following a recurrence. Further analysis of the participants unable to continue treatment between upfront therapy and first recurrence was associated with age $>$ 60 years and biopsy only, and age $>$ 60 years was associated with being unable to continue treatment between first and second recurrences. These high-risk patients may benefit from early BV initiation, while patients with good prognostic factors can tolerate delayed BV to a later progression.

In this retrospective analysis, delaying BV to later occurrences was not associated with diminished efficacy for either PFS or ST. The addition of cytotoxic chemotherapy to BV did not provide a survival benefit. Age and extent of resection identified patients who were unable to receive treatment at additional recurrences and describes a population that may not benefit from deferring BV initiation to later recurrences. Whether reserving BV for later recurrences improves survival should be evaluated prospectively. However, in properly selected patients, delaying BV therapy did not adversely affect its apparent efficacy.

Supplementary Material

Supplementary material is available online at Neuro-Oncology (http://neuro-oncology.oxfordjournals.org/).

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