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ORIGINAL REPORT

Phase II Study of Bevacizumab Plus Temozolomide During and After Radiation Therapy for Patients With Newly Diagnosed Glioblastoma Multiforme

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ABSTRACT

Purpose
This open-label, prospective, multicenter single-arm phase II study combined bevacizumab (BV) with radiation therapy (RT) and temozolomide (TMZ) for the treatment of newly diagnosed glioblastoma (GBM). The objectives were to determine the efficacy of this treatment combination and the associated toxicity.

Patients and Methods
Seventy patients with newly diagnosed GBM were enrolled between August 2006 and November 2008. Patients received standard RT starting within 3 to 6 weeks after surgery with concurrent administration of daily TMZ and biweekly BV. After completion of RT, patients resumed TMZ for 5 days every 4 weeks and continued biweekly BV. *MGMT* promoter methylation was assessed on patient tumor tissue. A University of California, Los Angeles/Kaiser Permanente Los Angeles (KPLA) control cohort of newly diagnosed patients treated with first-line RT and TMZ who had mostly received BV at recurrence was derived for comparison.

Results
The overall survival (OS) and progression-free survival (PFS) were 19.6 and 13.6 months, respectively, compared to 21.1 and 7.6 months in the University of California, Los Angeles/KPLA control cohort, and 14.6 and 6.9 months in the European Organisation for Research and Treatment of Cancer-National Cancer Institute of Canada cohort. Correlation of *MGMT* promoter methylation and improved OS and PFS was retained in the study group. Comparative subset analysis showed that poor prognosis patients (recursive partitioning analysis class V/VI) may derive an early benefit from the use of first-line BV. Toxicity attributable to RT/TMZ was similar, and additional toxicities were consistent with those reported in other BV trials.

Conclusion
Patients treated with BV and TMZ during and after RT showed improved PFS without improved OS compared to the University of California, Los Angeles/KPLA control group. Additional studies are warranted to determine if BV administered first-line improves survival compared to BV at recurrence.

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INTRODUCTION

Glioblastoma (GBM) is the most frequent and aggressive type of brain cancer. Based on the results of the phase III randomized trial[1] (European Organisation for Research and Treatment of Cancer [EORTC]/National Cancer Institute of Canada [NCIC]) comparing radiation therapy (RT) alone versus RT/temozolomide (TMZ) followed by six cycles of TMZ, adjuvant RT/TMZ has become established as the standard of care for newly diagnosed GBM and serves as the backbone for evaluating other first-line treatment strategies.[5]

Bevacizumab (BV) is a humanized monoclonal antibody directed against the vascular endothelial growth factor (VEGF). GBMs are highly vascularized tumors that heavily use proangiogenic factors such as VEGF for new blood vessel formation.[6] Recently, antiangiogenic therapy using BV alone or in combination with chemotherapies,

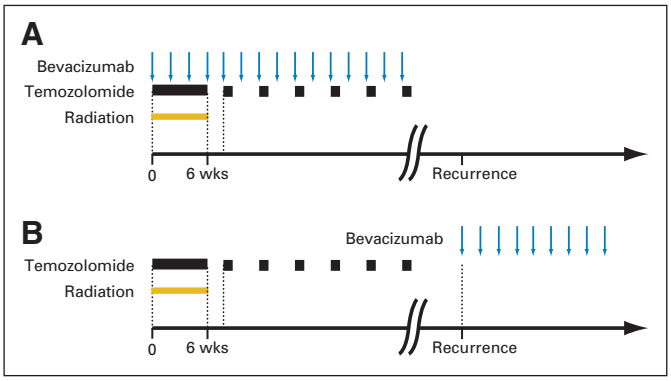

Fig 1. Treatment schema for (A) study group and (B) University of California, Los Angeles/Kaiser Permanente Los Angeles control group in which most patients received bevacizumab at recurrence. Wks, weeks.

such as irinotecan, has emerged as a promising development in the treatment of recurrent GBM.[3,7,8] Accelerated US Food and Drug Administration approval for the use of BV in recurrent GBM was obtained in May 2009.[9] The development of BV as a treatment option for recurrent GBM has raised the possibility that first-line treatment of newly diagnosed GBM with BV may be more advantageous than deferring BV until recurrence. To investigate whether BV would be safe and effective for the treatment of first-line GBM, we conducted a nonrandomized phase II trial combining BV with the current treatment for first-line GBM consisting of RT/TMZ (Fig 1A). Adverse events in the initial 10 patients have been previously reported.[10]

PATIENTS AND METHODS

Patient Selection

Eligibility criteria for this protocol included: ≥ 18 years of age, pathologically confirmed diagnosis of intracranial GBM including gliosarcoma by WHO criteria within 6 weeks of treatment, Karnofsky performance score (KPS) ≥ 60, and adequate organ function. All patients were newly diagnosed without prior treatment, including polifeprosan 20 with carmustine implant (Gliadel wafer, Eisai, Woodcliff Lake, NJ). Patients were required to have ≥ 200 mg of frozen tissue collected at surgery excluding most biopsy patients. Other standard exclusion criteria were applied. Patients requiring full-dose anticoagulation were not excluded. The protocol was approved by the University of California, Los Angeles institutional review board. All patients or their appointed surrogates signed the approved informed consent form.

Treatment Plan

Patients were treated with biweekly BV (10 mg/kg) administered intravenously and TMZ (75 mg/m^2) administered orally daily during RT (RT phase; Fig 1A). RT was started within 3 to 6 weeks after surgery. Each patient received thirty 2.0 Gy fractions, totaling 60.0 Gy. After completion of RT, BV was continued every 2 weeks. After a 2-week minimum interval after the last daily TMZ dose, patients were treated with biweekly BV and TMZ every 4 weeks at 150 to 200 mg/m^2/d for the first 5 days of every 28-day cycle until progression or for a maximum of 24 TMZ cycles (post-RT phase). For patients completing 24 cycles of TMZ, single-agent BV was continued every 2 weeks until progression. No dose modifications of BV were allowed, but delays of up to 90 days were allowed. The TMZ doses were adjusted primarily based on hematologic toxicities per package insert guidelines.

The pretreatment evaluation included a complete history, physical, and neurologic examination, and standard laboratory tests, obtained within 14 days of treatment. Baseline cranial magnetic resonance imaging was required within 3 weeks of treatment. Stained pathology slides were submitted for retrospective pathology confirmation. Formalin-fixed, paraffin-embedded tissue samples were analyzed for *MGMT* promoter methylation and *IDH1* genotype (Appendix, online only). Submitted frozen tissue samples were stored.

During the RT phase, a CBC was performed weekly, and blood chemistries were performed every 2 weeks. During the post-RT phase, a CBC was performed at weeks 2, 3, and 4 after the start of each 28-day TMZ cycle, and blood chemistries were performed every 2 weeks. A protein:creatinine ratio on spot urinalysis was performed at week 4 during RT, then every 8 weeks post-RT. General and neurologic examinations were performed every 2 weeks with specific attention to wound healing. Surveillance cranial magnetic resonance imaging was performed 2 weeks after the completion of radiation, and then every 8 weeks while patients were receiving treatment.

All patients were observed for overall survival (OS) and progression-free survival (PFS). Patients who experienced disease progression were observed for survival every 4 months.

Evaluation of Response

The primary end point was OS defined as the date of diagnosis to date of death from any cause. For patients lost to follow-up without obtainable date of death, censoring date was last clinic visit or contact. The secondary end point was PFS defined as the date of diagnosis to the date progressive disease was first observed. Unblinded central review using modified Levin criteria were used to evaluate imaging progression retrospectively and backdated to earliest sustained worsening of any assessable disease of larger than 1 cm change (based on T1 with contrast or T2 areas of tumor) or appearance of any new lesion/site (T1 with contrast or T2) of larger than 1 cm.[11] Progression was also determined clinically if the patient was placed on hospice, showed clinical decline measured by irreversible decrease in KPS lower than 50, or was unable to receive treatments due to clinical condition or death. If there was early treatment discontinuation due to serious adverse event, progression was called at time of imaging or clinical progression. In one case, a patient was taken off-study to participate in a vaccine trial and was censored at the time of off-treatment. For determination of PFS in a patient lost to follow-up, the censoring date was assigned based on the latest stable magnetic resonance imaging unless death from any cause occurred within 2 months of this magnetic resonance imaging in which case progression was called at death.

Statistical Plan

The primary and secondary end points were OS and PFS, respectively. Sample size calculation was based on the goal of increasing the 18-month survival rate from 40% (as reported by EORTC-NCIC) to 55%. Seventy patients provided 82% power using a one-sided α of .05. A 10-patient pilot phase was incorporated into the trial to detect unanticipated toxicities due to the combination of BV with RT and TMZ.[10] For these patients, a stopping rule specified study termination if the discontinuation rate owing to toxicity was ≥ 30% (three patients).

For the final analysis, results were compared with those derived from a comparable control cohort of patients treated at University of California, Los Angeles and Kaiser Permanente Los Angeles (KPLA) who received standard of care RT and TMZ followed by TMZ for up to 24 cycles. Of note, most of these control patients who required recurrent treatment received BV at some point after TMZ failure (Fig 1B). Recursive partitioning analysis (RPA) class determination[2] was performed retrospectively using age, KPS at treatment, extent of resection, and mental status (Appendix Fig A1, online only). Follow-up time was determined as the median of time of diagnosis to cutoff date (November 2009). OS was estimated using the Kaplan-Meier method. The Cox proportional hazards regression model was used to estimate unadjusted and adjusted hazard ratios (HRs) between the study and University of California, Los Angeles/KPLA control groups. Fleming(p,q) -weighted log-rank analysis was used to determine the significance when Kaplan-Meier curves crossed.[12] SAS 9.2 TS (SAS Institute, Cary, NC) was used for all statistical analysis.

RESULTS

Patient Demographics and Accrual

Seventy newly diagnosed patients with GBM (including 10 pilot phase patients) were registered between August 2006 and November 2008. Central pathologic review (O.E.S, W.H.Y) confirmed diagnosis of GBM in 70 patients. All patients were eligible and assessable. The median survival follow-up was 24.2 months. The University of California, Los Angeles/KPLA control group represented 110 patients initiating treatment between January 2005 and June 2007 with the median survival follow-up of 41.8 months. Patient characteristics of the study, University of California, Los Angeles/KPLA, and EORTC-NCIC groups are presented (Table 1). The study and control groups were well matched regarding median age and *MGMT* status. The study group had fewer biopsy patients and fewer RPA class III patients compared to the University of California, Los Angeles/KPLA group. The majority of University of California, Los Angeles/KPLA patients who recurred and received further treatment were given BV at some point.

Survival

For the primary end point, OS was 19.6 months (95% CI, 16.1 to 23.3 months) compared to 14.6 months for the EORTC-NCIC study. The 18-month OS rate was 54% (95% CI, 43% to 67%) compared to

Table 1. Patient Characteristics

Characteristic	Current Study RT/TMZ/BV (n = 70)		UCLA/KPLA Control RT/TMZ (n = 110)		EORTC-NCIC RT/TMZ (n = 287)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Enrollment by site						
UCLA	38	54	61	55	—	—
Kaiser	32	46	49	45	—	—
Age, years						
Median	57.4		59.4		56	
Range	31.3-75.8		20.5-90		19-70	
< 50	15	21	30	27	95	33
≥ 50	55	79	80	73	192	67
Sex						
Male	39	56	70	64	185	64
Female	31	44	40	36	102	36
Karnofsky performance status						
100	8	11	13	12	—	—
90	27	39	62	56	—	—
80	27	39	23	21	—	—
70	5	7	8	7	—	—
60	3	4	4	4	—	—
Extent of surgery						
Biopsy	2	3	23	21	48	17
Subtotal resection	40	57	40	36	126	44
Gross total resection	28	40	47	43	113	39
Recursive partitioning analysis by class						
III	9	13	27	25	42	15
IV	32	46	45	41	152	53
V	29	41	37	34	93	32
VI	0	0	1	1	0	0
Follow-up, months						
Median	24.2		41.8		61	
Range	12-40		29-58		—	
Deaths	48	69	89	81		
Recurrent treatment						
Progressed	56	80	96	87	272	95
Progressed with chemotherapy	39	56	64	58	148	52
Progressed with BV	29	41	57	52	—	—
MGMT promoter methylation						
Methylated	29	41	28	39	46	43
Unmethylated	41	59	43	61	60	57
IDH1 mutational status						
Wild type	65	93	68	96	—	—
R132H	5	7	3	4	—	—

Abbreviations: RT, radiation therapy; TMZ, temozolomide; BV, bevacizumab; UCLA, University of California, Los Angeles; KPLA, Kaiser Permanente Los Angeles; EORTC, European Organisation for Research and Treatment of Cancer; NCIC, National Cancer Institute of Canada; *MGMT*, O^6-methylguanine DNA methyltransferase; *IDH1*, isocitrate dehydrogenase 1.

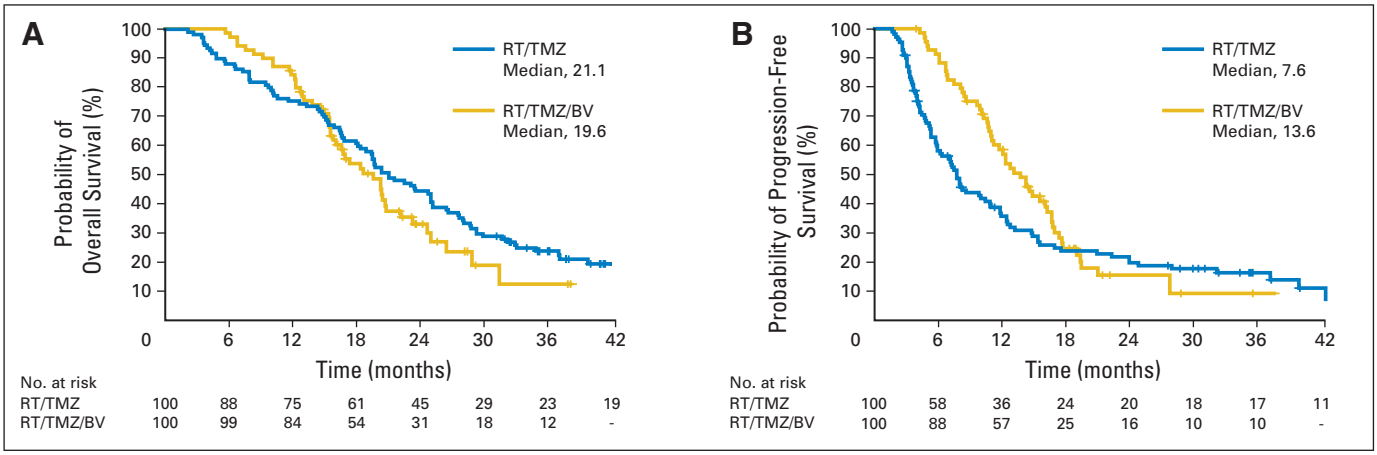

Fig 2. Kaplan-Meier analysis of (A) overall survival and (B) progression-free survival comparing current study group (gold; radiation therapy [RT] + temozolomide [TMZ] + bevacizumab [BV]) with University of California, Los Angeles/Kaiser Permanente Los Angeles control group (blue; RT + TMZ). Use of first-line BV shows early benefit in progression-free survival [Fleming(1,0) weighted log-rank test $P < .005$] and trended toward worse overall survival with later follow-up [Fleming(0,1) weighted log-rank test $P < .06$].

40% for the EORTC-NCIC study and approached the goal set in the statistical plan. However, the University of California, Los Angeles/KPLA control had OS of 21.1 months (95% CI, 18.9 to 25.2 months) with 18-month OS rate of 61% (95% CI, 52% to 71%; Fig 2A). Specifically, the OS curves crossed at approximately 15 months, and Fleming(0,1) log-rank analysis emphasizing survival after 15 months favored the University of California, Los Angeles/KPLA group ($P = .06$). The cross-over may be partly due to the higher number of RPA class III patients in the University of California, Los Angeles/KPLA control.

For the secondary end point, PFS for the study group was 13.6 months (95% CI, 11.1 to 16.5 months) compared to 7.6 months (95% CI, 5.9 to 10.8 months) for the University of California, Los Angeles/KPLA group (Fig 2B). This difference was significant using the Fleming(1,0) log-rank test emphasizing PFS before cross-over at approximately 18 months ($P < .005$). The PFS reported for the EORTC-NCIC study was 6.9 months for the RT/TMZ arm. The PFS at 6 months was 88% (95% CI, 82% to 96%) in the study group compared to 58% (95% CI, 50% to 68%) in the University of California, Los Angeles/KPLA group.

We derived multivariate Cox proportional hazard models for both OS and PFS initially using treatment, sex, promoter methylation of *MGMT*, and RPA class (III/IV *v* V/VI). The final models for OS and PFS did not include the treatment (Table 2). For OS, we found that female sex (HR, 0.66; $P < .05$), *MGMT* promoter methylation (HR, 0.49; $P < .001$), and RPA class III/IV (HR, 0.50; $P < .001$) were significant. For PFS, we found that female sex (HR, 0.59; $P < .01$) and *MGMT* promoter methylation (HR, 0.47; $P < .001$) were significant with RPA class III/IV trending toward significance.

We performed a prespecified subset analysis of the significant variables included in the Cox proportional hazards model to identify subgroups differing in OS between the study and University of California, Los Angeles/KPLA groups. In the study group alone, we found that the median OS and PFS for patient with *MGMT* promoter methylation was 24.7 and 17.5 months, respectively, compared to 15.9 and 10.5 months for those without *MGMT* promoter methylation (Appendix Fig A2, online only). However, the *MGMT* unmethylated group appeared to do more poorly for the study group than the control group as determined by Fleming(0,1) log-rank test emphasizing later follow-up ($P < .005$; Fig 3A), suggesting that BV does not rescue the *MGMT* unmethylated group previously shown to derive little benefit from TMZ.[13] In contrast, we observed that the combined RPA V/VI subgroup showed improved OS in the study group compared to the control group as determined by the Fleming(2,0) log-rank test emphasizing early follow-up ($P < .05$; Fig 3D). When components of the RPA analysis were examined separately, we found that patients younger than 50 years performed significantly less well in the study group compared to the control group (Fig 3E). When comparing male or female patients, male patients did slightly less well while no difference was seen in female patients (not shown).

Table 2. Cox Proportional Hazard Analysis of Treatment Group

	Progression-Free Survival		Overall Survival	
Parameter	Hazard Ratio	*P*	Hazard Ratio	*P*
Sex, female	0.59	.0091	0.66	.0449
MGMT, methylated	0.47	.0002	0.49	.0008
RPA class, III/IV	0.68	.0550	0.50	.0006

Abbreviations: *MGMT,* O^6-methylguanine DNA methyltransferase; RPA, recursive partitioning analysis.

Toxicity and Safety: Treatment Delivery

Based on planned interim safety evaluation of the 10 pilot phase patients,[10] we continued accrual to completion. No grade 5 events related to treatment were observed. Overall, treatment delivery characteristics were similar to the EORTC-NCIC trial (Appendix Table A1, online only). There appeared to be decreased RT interruption/delay compared to the EORTC-NCIC trial. The hematologic toxicity occurring during the RT or post-RT phase was compared for the three groups (Appendix Table A2, online only). The overall hematologic toxicities for the study group within the RT phase were comparable to

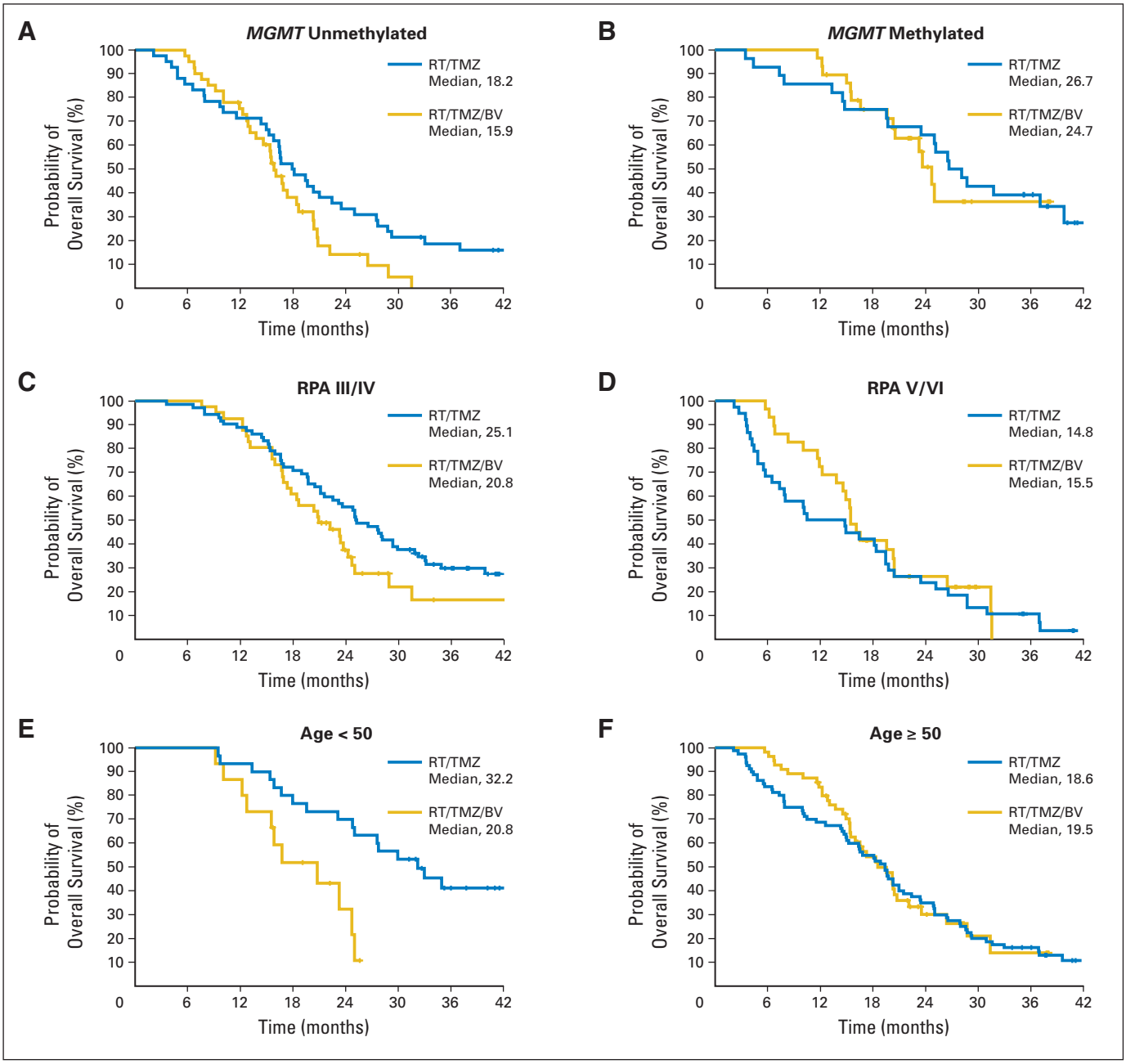

Fig 3. Prespecified Kaplan-Meier analysis of overall survival comparing current study (gold) and University of California, Los Angeles/ Kaiser Permanente Los Angeles (KPLA) control (blue) groups for (A,B) *MGMT* methylation, (C,D) recursive partitioning analysis (RPA) class, and (E,F) age. (A) Unmethylated *MGMT* promoter subgroup appears to do less well with the addition of bevacizumab (BV) in first-line treatment [(Fleming(0,1); $P < .005$], while showing no difference within the (B) methylated subgroup [Fleming (1,0); $P = .83$). (D) RPA V/VI group shows early benefit from the treatment compared with University of California, Los Angeles/KPLA control [Fleming(2,0) $P < .05$), while showing no difference within the RPA III/IV group (C) [Fleming(0,1) $P = .10$]. (E) Patients with age younger than 50 years did significantly less well with BV compared to the University of California, Los Angeles/KPLA control group (log-rank $P < .005$), without any difference in the (F) older than 50 years group [Fleming(1,0); $P = .42$]. RT, radiation therapy; TMZ, temozolomide.

both University of California, Los Angeles/KPLA and EORTC-NCIC control groups, indicating that the addition of BV to RT and TMZ did not potentiate hematologic toxicity. During the post-RT phase, increased incidence of neutropenia and thrombocytopenia were observed in the study group compared to the University of California, Los Angeles/KPLA control (comparison to EORTC-NCIC control is confounded by shorter maximum duration of TMZ usage in this study) with a decreased number of patient able to achieve full dose of maintenance TMZ.

Selected nonhematologic toxicities (grade 3 and 4) for the study were tabulated (Table 3). The most common nonhematologic treatment related toxicities were fatigue, followed by venous thrombosis, hypertension (HTN), and proteinuria. As far as other BV-related toxicities, we observed six cases (8.5%) of cerebrovascular ischemia, four wound infections, two GI perforations, and two GI bleeds. There were two CNS hemorrhages, one was a hemorrhagic subdural hematoma, and the other was a subarachnoid hemorrhage occurring after syncopal head trauma. There was one case of optic neuropathy, and

Table 3. Selected Nonhematologic Toxicity of Treatment Group

Adverse Event	No. of Patients		Grade 3 + 4	
	Grade 3	Grade 4	No.	%
CNS				
Cerebrovascular ischemia	0	6	6	9
Hemorrhage	1	1	2	3
Diarrhea	1	0	1	1
Dizziness/lightheadedness/syncope	5	0	5	7
Elevated ALT	2	1	3	4
Elevated AST	2	0	2	3
Elevated creatinine	1	0	1	1
Epistaxis	1	0	1	1
Fatigue	14	0	14	20
GI				
Bleed	2	0	2	3
Perforation	1	1	2	3
Hypertension	8	0	8	11
Hyperglycemia	7	0	7	10
Hypoglycemia	1	1	2	3
Hyponatremia	7	1	8	11
Ocular	1	1	2	3
Other infection	5	0	5	7
Proteinuria	6	2	8	11
Seizure	6	0	6	9
Venous thrombosis/pulmonary embolism	7	6	13	19
Wound infection	4	0	4	6

one case of retinal detachment. Comparison with toxicities from the EORTC-NCIC trial (Appendix Table A3, online only) shows similar levels of fatigue, headache, confusion, and vomiting.

DISCUSSION

In general, the study regimen was tolerable. There were no apparent increased or unanticipated toxicities attributable to the addition of BV in the radiotherapy phase. There were four wound infections, all occurring at the craniotomy site; three occurred during RT, with two associated with CSF leak, while one occurred 3 months after completion of RT. Most wound complications appeared associated with poor healing of the initial wound. Only two CNS hemorrhages were observed, neither were intraparenchymal, and one was clearly related to trauma while the other was an asymptomatic subdural hematoma. This suggests that inception of BV as early as 3 weeks after craniotomy does not increase risk of intraparenchymal hemorrhage but may potentiate wound problems in poorly healed wounds. We observed six cases of cerebrovascular ischemia (occurring between 83 and 538 days from date of surgery) based on detection of bright diffusion-weighted imaging lesions with corresponding low signal on the apparent diffusion coefficient map outside the tumor bed of which one was asymptomatically detected, as well as at least one other case occurring off-study but during BV treatment. Interestingly, all of these patients had pre-existing risk factors, such as HTN or hypercholesterolemia. Based on magnetic resonance imaging findings, the pattern of ischemia after BV treatment preferentially affects the small vessels, such as lenticulostriate perforating arteries, raising the possibility that BV potentiates radiation-induced occlusive arteriopathy. We suggest that reviewing DWI should be standard practice in all patients receiving BV, although accurate interpretation of such lesions will require further investigation. We observed 13 cases of venous thromboembolism and pulmonary embolism. Our experience, however, indicates that after treatment with anticoagulation (either warfarin or enoxaparin), patients can be safely resumed on treatment as we have reported for use of BV in the recurrent setting.[14] We observed grade 3 or 4 proteinuria in eight patients. These patients generally had a history of predisposing factor such as diabetes mellitus or HTN. In one patient the event was likely nonsteroidal anti-inflammatory drug induced, and in another vancomycin induced. In the remaining six patients, four were never restarted due to prolonged elevated urine protein:creatinine ratio, and two patients were able to restart only temporarily. Although based on small patient numbers, our experience indicates that holding BV treatment when the urine protein:creatinine ratio ≥ 2, and resumption when lower than 2 is preferable to allowing the urine protein:creatinine to exceed 3.5 before holding BV as stated in the protocol. Four patients had GI bleed or perforation while on study. Three of four had a predisposing factor such as prior GI surgery or diverticulosis. There was one previously reported case of optic neuropathy[10] that may be associated with BV but was difficult to definitely rule out tumor spread.[15] There was also one case of retinal detachment, which may be associated with BV and combination RT. Overall the toxicity signal of our trial was consistent with known toxicities of TMZ and BV,[4] without significant evidence of negative synergy with RT or TMZ, although relatively frequent occurrence of apparent cerebral ischemia requires more detailed study.

Since our study was not a randomized phase II study, we attempted to compare our study results to available historical data. The OS and PFS in the study group were improved compared to the EORTC-NCIC data. To control for any institutional treatment biases, such as the intention to treat patients with TMZ beyond the 6 months in the EORTC-NCIC protocol and differing salvage therapies, we derived a University of California, Los Angeles/KPLA control cohort of 110 patients. While the PFS for this group was similar to the EORTC-NCIC group, the OS of 21.1 months was significantly longer. However, this value is similar to a more recent group of RT/TMZ treated newly diagnosed GBMs.[16] Closer examination of the University of California, Los Angeles/KPLA cohort revealed that not only did a higher percentage receive salvage therapy but 56 (51%) received BV at recurrence (represented 89% of all patients that recurred and received further treatment) and may contribute to this difference in OS. Thus, comparison of the study group with the University of California, Los Angeles/KPLA control provides preliminary insight into the question of whether first-line BV is superior to recurrent BV in terms of OS. The increased PFS compared to the University of California, Los Angeles/KPLA control suggests a benefit of BV in prolonging PFS. However, the apparent lack of benefit in terms of OS suggests that BV at progression may provide the same OS benefit of BV first-line.

From our subgroup analysis, we found that the poor RPA class (V/VI) appeared to derive early benefit from upfront BV compared to the University of California, Los Angeles/KPLA control. This suggests that clinically determined poor prognosis patients may benefit from first-line treatment of BV which mirrors the improvement seen in PFS. When we examined age (< 50 or ≥ 50), we found a strikingly worse outcome ($P < .005$) for age younger than 50 patients (approximately 30% of adult GBMs) in the study group versus the control

group. In terms of molecular analysis, we assessed *MGMT* methylation on paraffin samples from each patient and found *MGMT* methylation was strongly associated with improved PFS and OS in the study. However, poor prognosis *MGMT* unmethylated patients (approximately 60% of adult GBMs) appeared to perform less well in the study group than control group [Fleming(0,1) $P < .005$].

In conclusion, we found that the addition of BV to RT/TMZ first-line therapy was tolerable without apparent unanticipated toxicities. In general, nonhematologic toxicities were similar compared to use of BV at recurrence with the exception of potentially greater incidence of arterial and venous thromboembolism.[3] While we observed improved PFS, the apparent lack of benefit in OS compared to University of California, Los Angeles/KPLA patients salvaged with BV awaits the results of ongoing large randomized studies (RTOG 0825 and Roche Avaglio [NCT00943826]) to determine whether the timing of BV impacts OS. If confirmed, these findings would have significant economic impact by sparing the cost of approximately 15 additional treatments. Correlative molecular and imaging studies are required to identify patients that will derive benefit from the addition of BV first-line.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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