Overview

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Title: Phase II Trial of Upfront Bevacizumab, Irinotecan, and Temozolomide for Unresectable Glioblastoma

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Lessons Learned

- Trials focusing on unresectable multifocal glioblastoma are needed because of the extremely poor prognosis and challenges in receiving standard therapy, such as concurrent radiation and chemotherapy.
- Developing a strategy to chemically debulk tumors before radiation and/or surgery is warranted.

Author Summary: Abstract and Brief Discussion

Background

Extent of resection remains a key prognostic factor in glioblastoma (GBM), with gross total resection providing a better prognosis than biopsy or subtotal resection. We conducted a phase II trial of upfront therapy with bevacizumab (BV), irinotecan (CPT-11), and temozolomide (TMZ) prior to chemoradiation in patients with unresectable, subtotally resected, and/or multifocal GBM.

Methods

Patients received up to 4 cycles of TMZ at 200 mg/m^2 per day on days 1–5 (standard dosing) and BV at 10 mg/kg every 2 weeks on a 28-day cycle. CPT-11 was given every 2 weeks on a 28-day cycle at 125 mg/m^2 or 340 mg/m^2 depending on antiepileptic drugs. Magnetic resonance imaging of the brain was done every 4 weeks, and treatment continued as long as there was no tumor progression or unmanageable toxicity. The primary endpoint was tumor response rate, with a goal of 26% or greater.

Results
Forty-one patients were enrolled from December 2009 to November 2010. Radiographic responses were as follows: 9 patients (22.0%) had partial response, 25 (61.0%) had stable disease, and 2 (4.9%) had progression; 5 patients were not assessed. Cumulative response rate was 22%. Median overall survival was 12 months (95% confidence interval: 7.2–13.5 months).

Conclusion
Upfront treatment with BV, TMZ, and CPT-11 is tolerable and can lead to radiographic response in unresectable and/or subtotally resected GBM.

Discussion
Standard treatment approaches for GBM result in median survival rates of between 8 and 16 months. Patients who have subtotal resection have a worse prognosis than patients who have gross total resection and an even worse prognosis than patients with unresectable/multifocal disease. In this phase II single-arm, single institution study (Duke University institutional review board approval Pro00019065; Clinical Trials.gov identifier NCT00979017), we evaluated the response rate of upfront TMZ, CPT-11, and BV in newly diagnosed unresectable GBM patients prior to standard chemoradiation. Secondary outcomes included safety and efficacy. Forty-one GBM patients were enrolled. The treatment plan prior to standard chemoradiation included four 28-day cycles of TMZ 200 mg/m^2 (days 1–5), BV 10 mg/kg, and CPT-11 125 mg/m^2 for patients taking a non-enzyme-inducing antiepileptic drug, or no antiepileptic drug (AED); CPT-11 dose was increased to 340 mg/m^2 for patients on an enzyme-inducing AED (on days 1 and 15). Brain magnetic resonance imaging was done every 4 weeks, with results interpreted according to published Response Assessment in Neuro-Oncology criteria. Patients were regularly monitored for treatment-related toxicities and disease-related morbidity.

The surgical extent for the study population was biopsy in 70.7% and subtotal resection in 29.3%. Most patients (70.7%) had only a biopsy, and 7 patients (17.1%) had multifocal disease. Fourteen patients completed all four planned cycles without tumor progression while on protocol. Thirty-six patients were evaluated for objective tumor response (Table 1). There were no complete responses and 9 partial responses, for an overall response rate of 22% (95% confidence interval [CI]: 12%–37%). Median follow-up for all patients was 41.7 months (95% CI: 32.3–46.1 months). Median overall survival was 12 months (95% CI: 7.2–13.5 months), and median progression-free survival was 8.6 months (95% CI: 3.5–11.3 months).

This multimodality approach to upfront treatment of patients with unresectable GBM consisting of the addition of anti-VEGF therapy with BV to TMZ and CPT-11 can provide disease control prior to radiotherapy. This combination regimen was tolerable, with no unexpected toxicities.

Trial Information

Disease	Brain cancer - primary
Stage of disease / treatment	Neoadjuvant
Prior Therapy	None
Type of study - 1	Phase II
Type of study - 2	Single Arm
Primary Endpoint	Overall Response Rate
Secondary Endpoints	Toxicity Progression-free Survival Overall Survival Incidence and Severity of CNS Hemorrhage and Systemic Hemorrhage
Additional Details of Endpoints or Study Design	For the primary endpoint, response rate for temozolomide alone was 42%, with a 95% CI of 26%–59%. If the true response rate with the combination upfront therapy was 26% or greater, then there would be interest in formally incorporating bevacizumab, irinotecan, and temozolomide upfront for the treatment of newly diagnosed GBM.
Investigator's Analysis	Some activity but insufficient for further development

Drug Information

Drug 1 **Generic/Working name**	Bevacizumab
Trade name	Avastin
Company name	Genentech
Drug type	Antibody
Drug class	Angiogenesis - VEGF
Dose	10 mg/kg
Route	IV
Schedule of Administration	Days 1 and 15 in 28-day cycle × 4 cycles
Drug 2 **Generic/Working name**	Irinotecan
Drug type	Chemotherapy
Drug class	Topoisomerase I
Dose	See Schedule of Administration
Route	Intravenous
Schedule of Administration	Given intravenously on days 1 and 15 at 125 mg/m^2 for patients on no antiepileptic or non-enzyme-inducing antiepileptics or 340 mg/m^2 for patients on enzyme-inducing antiepileptics on a 28-day cycle for 4 cycles
Drug 3 **Generic/Working name**	Temozolomide
Trade name	Temodar
Company name	Merck
Drug type	Chemotherapy
Drug class	Alkylating agent
Dose	200 mg/m^2
Route	Oral (po)
Schedule of Administration	Days 1–5 in 28-day cycle × 4 cycles

Patient Characteristics

Number of patients, male	18
Number of patients, female	23
Stage	Not applicable to primary brain tumors
Age	Mean (SD): 58 (10.2)
Number of prior systemic therapies	None
Performance Status	ECOG • 0 — 2 • 1 — 29 • 2 — 10 • 3 — 0 • Unknown — 0
Cancer Types or Histologic Subtypes	Glioblastoma 41

Primary Assessment Method

Control Arm: Glioblastoma

Number of patients screened	8
Number of patients enrolled	41
Number of patients evaluable for toxicity	41

Number of patients evaluated for efficacy	36
Evaluation method	Response Assessment in Neuro-Oncology (RANO)
Response assessment CR	$n = 0$ (0%)
Response assessment PR	$n = 9$ (22%)
Response assessment SD	$n = 25$ (61%)
Response assessment PD	$n = 2$ (4.9%)
Response assessment OTHER	$n = 5$ (12.1%)
(Median) duration assessments PFS	8.6 months
(Median) duration assessments OS	12 months

Adverse Events Adverse Events At All Dose Levels, Cycle 1

Name	*NC/NA	1	2	3	4	5	All Grades
Hemoglobin	98%	0%	0%	0%	2%	0%	2%
Blood/Bone Marrow - Febrile Pancytopenia	98%	0%	0%	0%	2%	0%	2%
Leukocytes (total WBC)	91%	0%	0%	2%	7%	0%	9%
Neutrophils/granulocytes (ANC/AGC)	91%	0%	0%	7%	2%	0%	9%
Platelets	66%	0%	0%	17%	17%	0%	34%
Fatigue (asthenia, lethargy, malaise)	93%	0%	0%	7%	0%	0%	7%
Death not associated with CTCAE term	93%	0%	0%	0%	0%	7%	7%
Rash/desquamation	98%	0%	0%	2%	0%	0%	2%
Rash: erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis)	98%	0%	0%	0%	2%	0%	2%
Colitis	98%	0%	0%	0%	2%	0%	2%
Hemorrhage, CNS	98%	0%	0%	2%	0%	0%	2%
Hemorrhage, GI	98%	0%	0%	2%	0%	0%	2%
Hemorrhage/Bleeding - Upper GI NOS	98%	0%	0%	2%	0%	0%	2%
Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC $<1.0 \times$ 10e9/L)	96%	0%	2%	0%	2%	0%	4%
Infection with normal ANC or Grade 1 or 2 neutrophils	90%	0%	0%	10%	0%	0%	10%
AST, SGOT(serum glutamic oxaloacetic transaminase)	98%	0%	0%	2%	0%	0%	2%
Potassium, serum-low (hypokalemia)	96%	0%	0%	2%	2%	0%	4%
Proteinuria	98%	0%	0%	2%	0%	0%	2%
Sodium, serum-low (hyponatremia)	93%	0%	0%	7%	0%	0%	7%
Confusion	98%	0%	0%	2%	0%	0%	2%
Seizure	88%	0%	0%	7%	5%	0%	12%
Thrombosis/thrombus/embolism	81%	0%	0%	2%	17%	0%	19%
Hemorrhage, GU	98%	0%	0%	2%	0%	0%	2%

Adverse Events Legend
Toxicity summary of all adverse events (all attributions).
*No Change from Baseline/No Adverse Event

Assessment, Analysis, and Discussion

Completion	Study completed
Pharmacokinetics / Pharmacodynamics	Not Collected
Investigator's Assessment	Some activity but insufficient for further development

Discussion

Although patients with GBM who have gross total resection achieve the best rates of OS, patients with suboptimal surgery and those for whom surgery is not possible at all have a worse prognosis [1–5]. Treatment regimens are needed that are

tailored to this poorly performing group. Upfront chemotherapy prior to or in lieu of radiation therapy has been used in neuro-oncology whether as a primary treatment or to chemically reduce the area before surgical intervention or radiation therapy [6–15]. The primary endpoint for our current study was to identify whether a significant radiographic response could be achieved in patients with an unresectable and/or subtotally resected tumor. In our study, an overall response rate of 22% was found. Previous studies using preirradiation chemotherapy regimens have been studied, and response rates have ranged from 13% to 54% and included the use of agents such as temozolomide (TMZ), carmustine with cisplatin, and carboplatin with etoposide [7–12]. Specific to our study, we enrolled only patients with multifocal and/or unresectable GBM, representing a subgroup of GBM with poorer prognosis. Response rate was 22%, and this met our criterion of an improvement exceeding 10%. Unfortunately, this did not reach our projected response rate of 26%. We have previously published a similar response rate in this population using an upfront regimen of 4 cycles of TMZ and bevacizumab (BV) at 24.4% [14]. Consequently, we concluded that this regimen of upfront therapy could provide radiographic disease control and stabilization before the initiation of radiotherapy for some patients, but our primary endpoint was not met.

Examining the subset of patients with unresectable disease, an additional important finding from the current study is that that upfront therapy with TMZ, BV, and irinotecan prolongs progression-free survival (PFS) of GBM patients. The median PFS of 8.6 months (95% confidence interval [CI]: 3.5–11.3 months) in our current study is an improvement on our prior findings of 3.1 months (95% CI: 1.4–8.7 months) in patients treated with TMZ and irinotecan without BV [16]. However, comparison of median overall survival (OS) outcomes of these two studies did not correlate with the PFS findings because the addition of BV to TMZ and irinotecan showed a worse outcome, with median OS of 12 months (95% CI: 7.2–13.5 months) in the current study versus median OS of 13.8 months (95% CI: 8.6–16.8 months) for TMZ and irinotecan alone [16]. Compared with our previous study with upfront TMZ and BV in a similar population, median OS was very similar. In this case, the addition of irinotecan resulted in OS of 12 months (95% CI: 7.2–13.5 months) versus 11.7 months (95% CI: 7.4–15.6 months) without irinotecan [14]. However, all three upfront combinations provided a substantial benefit for both PFS and OS compared with the subanalysis of similar unresectable, biopsy-only patients in prior studies (7.9 months for radiation alone and 9.4 months for chemoradiation in unresectable patients) [5]. A primary limitation of this current study and our two previous studies is that the sample size is quite small, so it will be challenging to compare these differences as significant.

A major limitation of the current study is that analysis of methylation of methyl guanine methyl transferase (MGMT) promoter was not obtained for all patients. In patients who underwent biopsy only, the amount of tumor tissue obtained was sometimes a limiting factor. To properly compare our results to our previous studies with upfront chemotherapy and to the historical Stupp regimen data, MGMT promoter methylation status should be determined. Moreover, compelling data from the multicenter GLARIUS study suggest that use of bevacizumab with irinotecan during radiotherapy is particularly beneficial to GBM patients that have nonmethylated MGMT promoter [17].

In conclusion, our multimodality approach to upfront treatment of patients with unresectable GBM consisting of the addition of anti-VEGF therapy with BV to TMZ and irinotecan can provide disease control prior to radiotherapy. Although we did not meet the endpoint for the trial, some partial responses to therapy were seen. Use of agents such as bevacizumab to control edema during radiation should be explored in this difficult-to-treat population. This combination regimen was tolerable with no unexpected toxicities.

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Figures and Tables

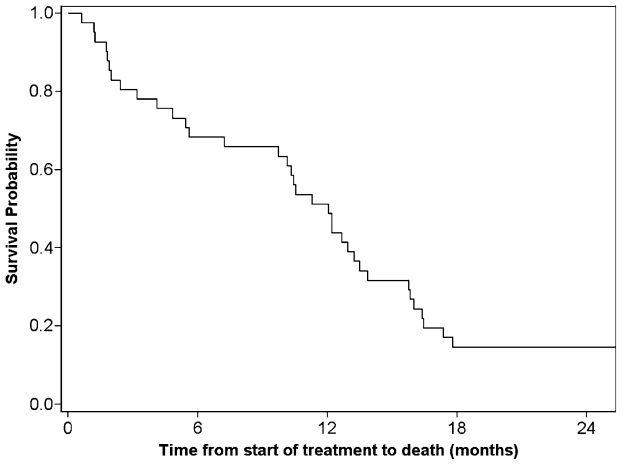

Figure 1. Kaplan-Meier plot for overall survival.

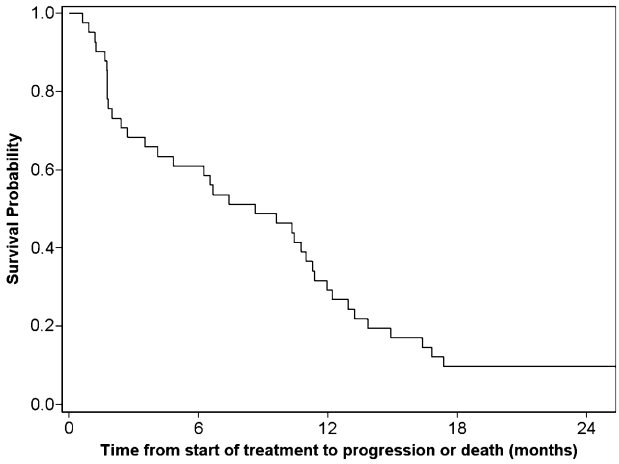

Figure 2. Kaplan-Meier plot for progression-free survival.

Table 1. Patient and clinical demographic characteristics

Characteristics	Results
Total patients, *N*	41
Age, years, mean (SD)	58 (10.2)
Sex, *n* (%)	
Male	18 (43.9)
Female	23 (56.1)
Karnofsky performance status, *n* (%)	
100	2 (4.9)
90	12 (29.3)
80	17 (41.5)
70	10 (24.4)
Surgery, *n* (%)	
Biopsy only	29 (70.7)
Subtotal resection	12 (29.3)
Extent of disease, *n* (%)	
Unifocal	34 (82.9)
Multifocal	7 (17.1)

Table 2. Overall best response as determined by the Response Assessment in Neuro-Oncology criteria

Response	Patients, *n*	%
Partial response	9	22.0
Stable disease	25	61.0
Progressive disease	2	4.9
Not assessed	5	12.1

Table 3. Survival estimates, reported as median time to survival from time of enrollment in trial until death or progression ($n = 41$)

Variable	Overall survival	Progression-free survival
Total patients, *N*	41	41
Failed, *n*	36	38
Median in months (95% CI)	12 (7.2–13.5)	8.6 (3.5–11.3)
6-month estimate, % (95% CI)	68.3 (51.7–80.2)	61.0 (44.4–74.0)
12-month estimate, % (95% CI)	51.2 (35.1– 65.2)	29.3 (16.4–43.4)
24-month estimate, % (95% CI)	14.6 (5.9–27)	9.8 (3.1–21)

Abbreviation: CI, confidence interval.

Table 4. Grade 3 and 4 adverse events related to treatment regimen of upfront bevacizumab, temozolomide, and irinotecan

	Number of events	
Toxicity	**Grade 3**	**Grade 4**
Hematologic		
Thrombocytopenia	7	5
Neutropenia	3	1
Leukopenia	1	3
Anemia	0	1
Nonhematologic		
Venous thromboembolism	1	7
Pneumonia	4	0
Hyponatremia	3	0
Fatigue	3	0
Gastrointestinal bleed	2	0
CNS hemorrhage	1	0
Colitis	0	1
Hematuria	1	0
Elevated AST	1	0
Hypokalemia	1	1
Proteinuria	1	0

Abbreviations: AST, aspartate aminotransferase; CNS, central nervous system.