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Clinical Trial Results

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

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Access the full results at: Peters-15-135.theoncologist.com

Author Summary

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.

Abstract

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 respons!e, 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. ***The Oncologist*** 2015; 20:727–728

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)

Discussion

Standard treatment approaches for GBM result in median survival rates of between 8 and 16 months. Patients who have

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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.

Author disclosures available online.

For Further Reading:

Myra E. van Linde, Joost J.C. Verhoeff, Dirk J. Richel et al. Bevacizumab in Combination With Radiotherapy and Temozolomide for Patients With Newly Diagnosed Glioblastoma Multiforme. ***The Oncologist*** 2015;20:107–108.

Abstract:

Background. Patients with a newly diagnosed glioblastoma multiforme (GBM) have a high risk of recurrent disease with a dismal outcome despite intensive treatment of sequential surgery and chemoradiotherapy with temozolomide (TMZ), followed by TMZ as a single agent. Bevacizumab (BV) may increase response rates to chemotherapy in the recurrent treatment setting of GBM. We hypothesized that a neoadjuvant treatment strategy for patients with newly diagnosed GBM using chemoradiotherapy plus BV would improve resectability and thus survival. We performed a phase II trial of the treatment strategy of BV plus chemoradiation to determine the safety of this combination in patients who had already undergone primary surgery for their GBM.

Methods. After a biopsy (6 patients) or a resection (13 patients) of a newly diagnosed GBM, 19 patients received radiotherapy (30 fractions of 2 Gy) in combination with daily TMZ 75 mg/m2 and BV 10 mg/kg on days 1, 14, and 28, followed by 6 monthly cycles of TMZ 150–200 mg/m2 on days 1–5.

Results. The overall response rate was 26%. Three patients had a complete response after resection, and in two patients, a complete response after resection followed by chemoradiation plus BV was seen. No grade 3–4 toxicities were observed during combination treatment. The median progression-free survival was 9.6 months (95% confidence interval [CI]: 4.3–14.4 months). The median overall survival was 16 months (95% CI: 8.1–26.3 months), similar to a matched control group that received standard chemoradiotherapy from our institution.

Conclusion. Combination of bevacizumab with radiotherapy and TMZ is safe and feasible in patients with newly diagnosed GBM, but because of low response rates, this treatment strategy does not favor a neoadjuvant approach.