Gamma Knife followed by bevacizumab effective for recurrent glioblastoma multiforme

by Douglas Kondziolka, MD; L. Dade Lunsford, MD; John C. Flickinger, MD; Hideyuki Kano MD, PhD; Frank Lieberman, MD

The treatment of recurrent glioblastoma multiforme (GBM) is challenging. Although re-irradiation is limited by the radiation tolerance of the brain, stereotactic radiosurgery can selectively boost the target tissue and the adjacent tumor border where most further recurrences develop. Several reports have described the potential efficacy and acceptable toxicity of radiosurgery for recurrent GBM.

GBMs are innately hypoxic tumors with strong endogenous expression of vascular endothelial growth factor (VEGF) which is a potent mitogen that facilitates migration, proliferation and survival of endothelial cells which are essential for tumor angiogenesis. VEGF is directly correlated with tumor growth rate, metastatic potential and poor outcome. Bevacizumab, a humanized monoclonal antibody to VEGF, inhibits angiogenesis and has been found to be active in several types of tumors such as breast, non-small cell lung cancer and colorectal cancer. A series of phase 2 trials employing bevacizumab and irinotecan demonstrated encouraging response rates, as well as improvements in time-to-progression and 6-month progression free survival in patients with recurrent malignant gliomas compared to historical controls. In the present study we evaluated the efficacy and safety of re-irradiation using Gamma Knife Stereotactic Radiosurgery (GKSR) followed by bevacizumab in a series of patients with recurrent GBM and compared outcomes to a matched cohort who underwent salvage GKSR alone.

Our experience included eight male and three female patients. The median patient age at GKSR was 62 years (range, 46-72 years). At the time of GKSR, seven patients had a first recurrence and four had two or more recurrences. The median interval from the initial diagnosis until GKSR was 17 months (range, 5-34.5 months). The median tumor volume was 13.6 cm³ (range, 1.2-45.1 cm³) and the median margin dose of GKSR was 16 Gy (range 13-18 Gy). Following GKSR, bevacizumab was administrated with irinotecan in nine patients and with temozolomide in one patient. One patient was treated with bevacizumab monotherapy. The treatment outcomes were compared to 44 case-matched controls who underwent GKSR without additional bevacizumab.

At a median of 13.7 months (range, 4.6-28.3 months) after radiosurgery, tumor progression was evident in seven patients. The median progression-free survival (PFS) was 15 months (95% Confidential Interval [CI], 6.5–23.3 months). Six-month and 1-year PFS rates were 73% and 55%, respectively. The median overall survival (OS) from GKSR was 18 months (95% CI, 10.1 – 25.7 months) and 1-year OS rate was 73%. One patient (9%) experienced grade III toxicity and one patient (9%) had major adverse radiation effects. Compared with patients who did not receive bevacizumab, the patients who received bevacizumab had significantly prolonged PFS (15 months vs. 7 months, p=0.035) and OS (18 months vs. 12 months, p=0.005), and were less likely to develop an adverse radiation effect (9% vs. 46%, p=0.037).

The combination of salvage GKSR followed by bevacizumab added potential benefit and little additional risk in a small group of patients with progressive glioblastoma. Further experience is needed to define the efficacy and long-term toxicity with this strategy.

Treatment Response and Survival

Post-treatment MRI scans were available for review on all 11 patients. The initial MRI at a median of 2 months (range: 1.5 months) after GKSR suggested tumor progression in two patients, stable disease in five patients, and partial response in four patients. Of the two patients with “progression” on the initial images, one was found to have a treatment response at the time of next follow up imaging, thus consistent with pseudoprogression (figure 1 above). The other patient did not undergo subsequent imaging due to clinical deterioration. During the median of 14 months of follow-up (range, 4.6 – 28.3 months) after GKSR, the best tumor response (based on RANO criteria) was complete response in two patients, partial response in five patients, stable disease in three patients and progressive disease in one patient. Over time, delayed tumor progression was evident in seven patients (63%). Treatment failure occurred within the radiosurgery volume in three patients and at adjacent area close to the margin of the treatment volume in two (figure 2 above). Two patients had a stable or smaller tumor compared with initial imaging but developed additional FLAIR or T2 signal change surrounding the radiosurgery target. The median PFS after GKSR was (continued on page 8)