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CLINICAL INVESTIGATION **Central Nervous System Tumor**

CHANGE IN PATTERN OF RELAPSE AFTER ANTIANGIOGENIC THERAPY IN HIGH-GRADE GLIOMA

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Purpose: Local recurrence is the dominant pattern of relapse in high-grade glioma (HGG) after conventional therapy. The recent use of antiangiogenic therapy has shown impressive radiologic and clinical responses in adult HGG. The preclinical data suggesting increased invasiveness after angiogenic blockade have necessitated a detailed analysis of the pattern of recurrence after therapy.

Methods and Materials: A total of 162 consecutive patients with HGG, either newly diagnosed (n = 58) or with recurrent disease (n = 104) underwent therapy with bevacizumab at 10 mg/kg every 2 weeks and conventional chemotherapy with or without involved field radiotherapy until disease progression. The pattern of recurrence and interval to progression were the primary aims of the present study. Diffuse invasive recurrence (DIR) was defined as the involvement of multiple lobes with or without crossing the midline.

Results: At a median follow-up of 7 months (range, 1–37), 105 patients had recurrence, and 79 patients ultimately developed DIR. The interval to progression was similar in the DIR and local recurrence groups (6.5 and 6.3 months, p = .296). The hazard risk of DIR increased exponentially with time and was similar in those with newly diagnosed and recurrent HGG (R^2 = 0.957). The duration of bevacizumab therapy increased the interval to recurrence (p < .0001) and improved overall survival (p < .0001). However, the pattern of relapse did not affect overall survival (p = .253).

Conclusion: Along with an increase in median progression-free survival, bevacizumab therapy increased the risk of DIR in HGG patients. The risk of increased invasion with prolonged angiogenic blockade should be addressed in future clinical trials. © **2012 Elsevier Inc.**

High-grade glioma, Bevacizumab, Antiangiogenic therapy, Chemoradiotherapy, Brain invasion.

INTRODUCTION

High-grade gliomas (HGGs), classified as World Health Organization (WHO) Grade III and IV tumors, represent the most common form of primary central nervous system tumors in adults (1). Current treatment has involved maximal surgical resection, followed by involved field radiotherapy (RT) and chemotherapy, with an expected survival time of 12–36 months (2). Although earlier attempts at using chemotherapy were often ineffective, the use of temozolomide in the treatment of newly diagnosed HGG has become the standard of care, given its effectiveness owing to its ability to cross the blood–brain barrier (3). Irinotecan and carboplatin have been other agents used in the treatment of recurrent HGG owing to their cytotoxic effects, although their ability to cross the blood–brain barrier is limited (4, 5).

In an effort to improve the outcomes, antiangiogenic therapy has been a focus of current research, with vascular endothelial growth factor (VEGF) as an important molecular target, given its role in angiogenesis (6). Bevacizumab (Avastin, Genentech, South San Francisco, CA) is a humanized monoclonal antibody against VEGF-A and is one of the first antiangiogenic inhibitors developed. It has been approved by the Food and Drug Administration for use against recurrent glioblastoma multiforme. Phase II-III trials of newly diagnosed HGG, in conjunction with RT and temozolomide (7, 8) are ongoing. The results of bevacizumab against recurrent HGG in several Phase II clinical trials have demonstrated a radiologic response rate of 47–67% and a 6-month overall survival rate of 62–77% (9, 10). In two small pilot trials of newly diagnosed HGG, bevacizumab, temozolomide, and RT were well-tolerated, with an acceptable level of observed toxicity and a radiologic response rate of 92% and 1-year progression-free survival rate of 59.3% (8, 11). However, evidence has suggested that both *in vitro* and *in vivo* VEGF blockade can induce

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a more invasive phenotype in HGG (12). Evidence suggesting a shift away from local recurrence (LR) to diffuse invasive recurrence (DIR) has been demonstrated in *in vitro* models, although large scale clinical trials have not yet shown this phenomenon in patients (13). The present study sought to demonstrate such a change after bevacizumab therapy in a clinical setting in both recurrent and newly diagnosed HGG patients.

METHODS AND MATERIALS

The institutional review board approved the retrospective analysis of the pattern of recurrence in 162 consecutive patients with HGG who had undergone bevacizumab therapy at New York University Langone Medical Center and Overlook Hospital (Summit, NJ) between March 2006 and July 2009. The preliminary clinical results of two separate trials using bevacizumab (a prospective study of newly diagnosed glioma and a retrospective study of recurrent glioma) have been previously reported (11, 14, 15). In the first study, all newly diagnosed HGG patients underwent maximal surgical resection, when feasible, at the initial diagnosis, followed by RT and temozolomide. Involved field radiation was administered at 1.8 Gy/fraction to a dose of 59.4 Gy using a conformal technique. Whole brain RT was administered at 2.67 Gy/fraction within 15 fractions to a dose of 40.05 Gy for 8 patients who had presented with multicentric disease at diagnosis. Temozolomide was given orally at 75 mg/m^2 on Days 1–42 of RT and at 150 mg/m^2 every 7 days for Days 1–28 at 1 month after chemoradiotherapy. Bevacizumab was administered intravenously at 10 mg/kg on Days 14 and 28 during RT and every 2 weeks thereafter until disease progression or the onset of dose-limiting toxicity. In the second study, all patients with recurrent HGG had undergone surgical resection, when feasible, at recurrence, followed by chemotherapy with intravenous irinotecan, at 125 mg/m^2, and intravenous bevacizumab, at 10 mg/kg, every 2 weeks until disease progression or the onset of dose-limiting toxicity. Carboplatin was given every 4 weeks to achieve an area under the curve of 6, along with bevacizumab therapy in patients previously treated with irinotecan.

The modified MacDonald criteria were used to define the radiologic response that included maximal cross-sectional T_1-weighted contrast images on magnetic resonance imagine and fluid attenuated inversion recovery (FLAIR) sequences (16). Progression was defined as a $\geq$25% increase in the size of a pre-existing, enhancing lesion, FLAIR changes, neurologic deterioration that could not be attributed to another cause. DIR was defined as recurrence involving multiple lobes or crossing the midline, with or without a component of local recurrence (Fig. 1). LR was defined as recurrence within a 2-cm margin of the original, primary tumor and/or confined to the lobe, because most tumors recur within this area (17, 18). Progression-free survival was measured from the start of bevacizumab treatment to the date of the first sign of clinical or radiologic progression. Overall survival was measured from the start of bevacizumab treatment to the date of death.

Patient age, tumor grade, choice of chemotherapy agent, and pattern of relapse were the variables considered in the present study. The patients who were alive at the last follow-up visit were considered as a censored event in the analysis. The progression-free survival and overall survival between the two groups were analyzed using the Kaplan-Meier estimates, and the log-rank test was used to test for equality of the survival distributions. Multivariate Cox proportional hazards models were used to estimate the effect of bevacizumab therapy on survival in the presence of the other known prognostic factors. Age, the pattern of relapse, and tumor grade were treated as covariates in the Cox model. The hazard ratios and their corresponding 95% confidence intervals were calculated, with adjustment for selected factors in the same model. p Values were determined using two-sided tests, and $p < .05$ was considered statistically significant. All statistical

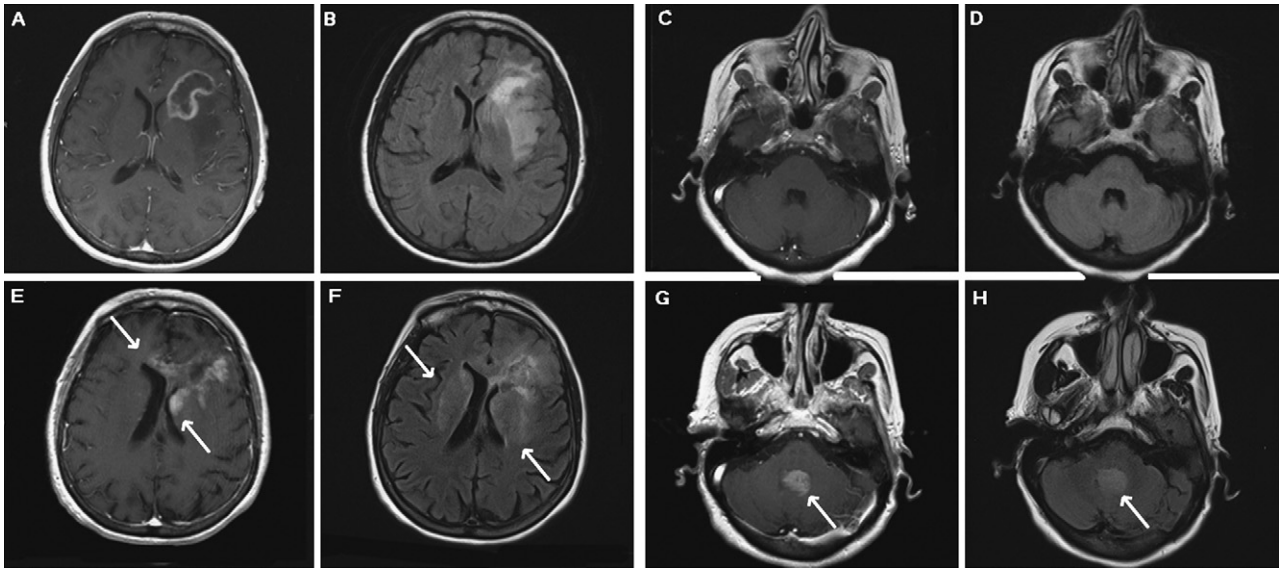

Fig. 1. Images of 72-year-old woman with glioblastoma of left frontal lobe who had undergone surgical resection, radiotherapy, and temozolomide therapy. Imaging before bevacizumab therapy at first relapse showed local recurrence at left frontal lobe (A, B), with little evidence of disease elsewhere (C, D). At 8 months after bevacizumab therapy, imaging revealed evidence of diffuse invasion across genu of corpus callosum into contralateral brain and into left temporal lobe (E, F). Additionally, abnormal enhancement detected within cerebellar vermis and peritrigonal white matter (G, H). Slides A, C, E, and G of T_1-weighted contrast images and B, D, F, and H of fluid attenuated inversion recovery images.