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CASE REPORT

Radiographic patterns of relapse in glioblastoma

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Abstract Glioblastoma (GBM) pathologically is defined as an infiltrative glioma and salvage therapy with bevacizumab is believed to increase the incidence of diffuse and distant invasion as assessed radiographically. Eighty adult patients with glioblastoma were treated with surgery followed by radiotherapy (RT) and concurrent and adjuvant temozolomide (TMZ). At first recurrence, 80 patients were treated with single agent bevacizumab. At time of progression, 57 patients were treated with bevacizumab and a cytotoxic chemotherapy, cytotoxic chemotherapy alone or on an investigational trial. Magnetic resonance imaging (MRI) were analyzed at four time points in each patient; at presentation, at first, second and third recurrence. Four patterns of radiographic disease were assessed, local (unifocal disease), distant (second lesion noncontiguous with primary lesion), multifocal (>2 lesions including leptomeningeal dissemination) and diffuse. At presentation 87.5% of glioblastoma were local, 6.25% distant, 3.75% multifocal and 2.5% diffuse. At first recurrence following progression on RT/TMZ and before initiation of bevacizumab, 80% were local, 7.5% distant, 6.25% multifocal (including 1 with CSF dissemination) and 6.25% diffuse. At second recurrence following progression on bevacizumab, 71.25% were local, 8.75% distant, 8.75% multifocal (2/7 with CSF dissemination) and 11.25% were diffuse. At third recurrence (57 patients evaluable), 71.25% were local, 7.0% distant, 7.0% multifocal and 14.0% were diffuse. Survival following progression on bevacizumab did not differ by pattern of radiographic recurrence. A majority of adult patients with GBM at diagnosis manifest MRI-defined local disease and maintain this pattern notwithstanding multiple recurrences and treatment with bevacizumab.

Keywords Patterns of relapse · Glioblastoma · Bevacizumab · Radiographic · MRI

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Introduction

Glioblastoma (GBM), the most common primary brain tumor in adults, remains a significant challenge to treat notwithstanding increasing utilization of the European Organization for Research and Treatment of Cancer/the National Cancer Institute of Canada (EORTC/NCIC) treatment platform (radiotherapy with concurrent and adjuvant temozolomide) at initial diagnosis followed by bevacizumab (BEV) at first recurrence [1–4]. This combination of treatment has gained wide acceptance in the United States as a standard of care for patients with GBM particularly amongst community-based oncologist with limited access to clinical trials. A perception in the neuro-oncology community is that treatment of recurrent GBM with the anti-vascular endothelial growth factor (VEGF) monoclonal antibody, bevacizumab, results in an increased incidence of distant and diffuse patterns of radiographic recurrence. These magnetic resonance imaging (MRI) defined patterns of relapse may include an appearance not unlike gliomatosis cerebri, in this context defined as secondary gliomatosis cerebri, and cerebral spinal fluid (CSF) dissemination, often termed meningeal gliomatosis.

This retrospective review of 80 adult patients with supratentorial GBM, all treated initially with radiotherapy

(RT) and concurrent and adjuvant temozolomide (TMZ) followed by single agent BEV at first recurrence were analyzed for patterns of radiographic presentation at four clinically relevant time points; presentation, first recurrence following progression on RT/TMZ and before initiating BEV, second recurrence following progression on single agent BEV, and third recurrence following salvage therapy that included re-resection, BEV plus a cytotoxic chemotherapy, cytotoxic chemotherapy only or an investigational trial.

Methods

Eighty adult patients (50 men; 30 women) with supratentorial GBM ranging in age from 19 to 78 years (median 57) were retrospectively analyzed with respect to MRI pattern of disease at four time points. Pattern of MRI defined disease at presentation and before surgery was noted as well as at three clinically relevant epochs following initial surgery and treatment with the EORTC/NCIC platform. Post-radiotherapy time points considered relevant were first, second and third recurrence. First recurrence was defined as progression after initial treatment with RT and TMZ and before initiation of first salvage therapy with single agent BEV. Second recurrence was defined as progression on single agent BEV and before initiation of an alternative therapy. Alternative therapy included a cytotoxic chemotherapy (25 patients), BEV plus a cytotoxic chemotherapy (22 patients) or an investigational trial (10 patients). Third recurrence was determined after progression on one of the above mentioned alternative therapies. MRI was performed at multiple time points in each patient and in general was performed prior to surgery and 24–72 h after surgery, 4 weeks after RT and every 2 months thereafter. All patients treated with BEV in addition were imaged 1 month after initiating BEV.

Patterns of MRI defined disease were characterized as local, distant, multifocal or diffuse utilizing the radiographic classification as defined by Pope and using data from the BRAIN trial, a prospective Phase II non-comparative trial of BEV with or without irinotecan for the treatment of recurrent GBM [5]. Local disease (contrast enhancing or not) was defined as unifocal, contiguous with the primary site or resection cavity and within a 3 cm margin. Distant disease (contrast enhancing or not) was defined as a second non-contiguous lesion in addition to disease (stable or other) at the primary site. Multifocal disease was defined as three or more non-contiguous lesions (contrast enhancing or not) including the primary site. CSF spread of disease was operationally defined as multifocal disease. Diffuse disease was defined as disease (enhancing or not) extending greater than 3 cm beyond the primary site, frequently challenging to quantify due to poor or indistinct contrast or FLAIR margins.

Institutional review board approval was obtained for the retrospective MRI analysis.

Results

At presentation, 87.5%:70/80 of patients presented with unifocal disease defined operationally as local disease as determined by pre-surgery MRI (Table 1). The remaining 12.5%:10/80 of patients were portioned between distant, multifocal and diffuse MRI defined radiographic patterns in which one-third were contrast enhancing and two-thirds non-contrast enhancing. Following initial treatment with RT and TMZ, before initiating single agent BEV and at first recurrence, 8.5%:6/70 of patients with initial local disease converted to distant, multifocal or diffuse patterns (2/6 contrast enhancing; 4/6 non-contrasting enhancing). Eighty patients were evaluable for pattern of relapse following progression on RT and TMZ and before introduction of BEV. 18.75%:15/80 patients before initiation of BEV underwent a re-resection for recurrent and progressive disease. Median time to initiating BEV was 8 months from initial surgery.

At second recurrence (all 80 patients radiographically assessable; median time from initiation of BEV to BEV failure 5.5 months) following treatment with single agent BEV, 12.5%:8/64 of patients converted to distant, multifocal or diffuse patterns (3/8 contrast enhancing; 5/8 non-contrast enhancing). Following treatment and progression on BEV, 23 patients (28.75%) elected to discontinue all further treatment and were admitted to hospice. Within this group of patients electing supportive care, 15 demonstrated a local recurrence pattern (12/15 contrast enhancing; 3/15 non-enhancing) following BEV progression as did 3 patients each with distant or multifocal recurrence pattern (2/6 contrast enhancing; 4/6 non-contrast enhancing) and 2 patients with a diffuse recurrence (all contrast enhancing). Median survival in this group was 1.4 months (0% 6-month progression free survival).

At third recurrence (57 total evaluable patients) and following treatment with re-resection (8.8%:5/57), BEV plus chemotherapy (38.6%:22/57), an investigational trial (17.5%:10/57) or another chemotherapy (44%:25/57) converted from a local to a diffuse non-enhancing pattern. Patients with an initial pattern of disease other than local (i.e. distant, multifocal or diffuse), did not change their MRI defined pattern of disease on third relapse. Median survival in this group was 3.2 months and survival did not differ with respect to pattern of radiographic relapse (local recurrence; median survival 3.3 months after BEV only progression: non-local recurrence; median survival

Table 1 Neuroradiographic patterns of relapse

Pattern/time	Presentation ($n = 80$)	First recurrence [post-TMZ + RT, onset BEV] ($n = 80$)	Second recurrence [progression on BEV only] ($n = 80$)	Third recurrence [progression on BEV + or alternative] ($n = 57$)
Local	70 (87.5%)	64 (80%)	57 (71.3%)	41 (71.9%)
Local to other		6 (8.5%)	8 (12.5%)	1 (1.75%)
Distant	5 (6.25%)	6 (7.5%)	7 (8.75%)	4 (7.0%)
Multifocal	3 (3.75%)	5 (6.25%)	7 (8.75%)	4 (7.0%)
Diffuse	2 (2.5%)	5 (6.25%)	9 (11.25%)	8 (14.0%)

TMZ temozolomide; *RT* radiotherapy; *BEV* bevacizumab; *Other* distant, multifocal or diffuse

2.9 months). Overall 6-month progression free survival was 0% in this cohort of 57 patients.

Across the entire group of 80 patients, the only change in radiographic pattern was seen in patients with initial local disease (70/80 patients) in whom 21.4% (15/70 patients) converted to an alternative pattern and in the majority (53%; 8/15 patients) this new pattern was diffuse disease. There were no patients that manifested a combination pattern of relapse (such as local + diffuse) perhaps due to small numbers of patients evaluated. Amongst the 8 patients changing to a diffuse pattern at recurrence, similar numbers of patients converted at first ($n = 3$), second ($n = 4$) and third recurrence ($n = 1$). The change to a diffuse pattern did not appear time on treatment dependent (similar in patients responding to BEV compared to patients not responding). All patients with a diffuse pattern at time of third recurrence (8/57) were treated with non-bevacizumab containing regimens. In 4/10 patients (40%) with a diffuse pattern of recurrence, involvement of three or more cerebral lobes was noted fulfilling the operational definition of secondary gliomatosis cerebri. In two of these four patients, the occurrence of gliomatosis cerebri occurred at time of progression on a bevacizumab containing regimen. In only two patients was a conversion seen to leptomeningeal spread of disease (both defined as multifocal disease; one determined at first recurrence before initiation of BEV and the other at second recurrence following treatment with single agent BEV). Extent of surgical resection (complete, partial or biopsy) at any time point (initial surgery or re-resection for recurrent disease) did not appear to impact the pattern of recurrence, i.e. similar probability of local recurrence versus other pattern of recurrence.

Discussion

Patterns of disease recurrence following treatment with the EORTC/NCIC platform as well as bevacizumab containing regimens at recurrence have been recently characterized by Pope from the prospective BRAIN trial as well by Norden, Oh and Iwamoto in single institution retrospective reviews [5–9] (Table 2). Problematic in determining patterns of radiographic relapse in gliomas is defining categories of relapse as these definitions determine incidence of a stated pattern of relapse. At present there has not been universal agreement on definitions of relapse and consequently there is variability on what constitutes a given pattern of relapse. The present study utilized definitions of radiographic relapse as defined by Pope as these were well characterized, easily emulated, but not yet validated in a prospective trial and potentially biased as determinations were made by a single reader. Further confirmation of the Pope criteria for patterns of radiographic relapse will be evaluated in the Radiation Treatment Oncology Group up-front trial of bevacizumab for newly diagnosed GBM. Pope delineated four radiographic patterns of disease (local, distant, multifocal and diffuse) in a retrospective analysis of the prospective BRAIN trial of 167 patients with recurrent GBM treated with BEV and with or without irinotecan [5]. At baseline, following treatment with TMZ and RT and before BEV, 72% of patients manifested local disease at recurrence. Seventeen percent were diffuse, 2.4% distant and 8% were multifocal at recurrence before initiation of BEV. Following treatment with BEV, 82% of patients showed no change in disease pattern. The only change noted was enrichment of the diffuse category wherein 11 patients (16%) in the baseline local group converted to a diffuse pattern. Pope concluded that shift of radiographic pattern at time of institution of BEV was uncommon and the majority of patients maintained baseline pattern noted at recurrence and before institution of BEV. This data in part dispels the perception that anti-angiogenic therapy increases the proportion of patients with non-localized disease at progression. As well, the report suggests non-local disease recurrence of GBM following initial therapy with RT + TMZ is more common (28%) than appreciated and appears to be the natural progression of treated GBM. Also the study indicated that survival did not appear different amongst the radiographic patterns of recurrent disease

Table 2 Neuroradiographic patterns of relapse based on the literature

	Pope ($n = 167$)		Norden ($n = 26$)		Oh ($n = 67$)		Iwamoto ($n = 37$)	
	Local	Other	Local	Other	Local	Other	Local	Other
Prior to BEV (%)	72	28	NS	NS	86.5	13.4	NS	NS
After progression on BEV (%)	82	18	62	38	NS	NS	46	54

BEV bevacizumab; *NS* not stated

(local to local median overall survival 9.7 months; local to diffuse median overall survival 9.3 months). Not evaluated in this study however was the pattern of disease at presentation and prior to initial surgery or the pattern of disease progression following BEV failure. In addition survival following BEV failure was not commented upon.

Norden retrospectively evaluated 55 patients with high-grade gliomas treated with BEV and irinotecan [6, 7]. Twenty-three patients were treated at BEV recurrence with BEV plus a different cytotoxic chemotherapy and median progression free survival was 7 weeks. Twenty-six patients were evaluated for pattern of disease progression following progression on BEV and 64% were local, 18% were distant and 18% were diffuse. Not stated were the definitions of radiographic patterns of recurrent disease or the pattern seen prior to initiation of BEV. In a small control group of patients ($n = 16$) not treated with BEV, Norden reported similar patterns of radiographic recurrence (68% local, 16% diffuse and 6% distant) concluding that pattern of relapse did not statistically appear different when comparing BEV based therapies to non-BEV based salvage therapy.

Oh reviewed 111 adult patients with newly diagnosed supratentorial GBM amongst which 67 had disease recurrence that was evaluable by MRI [8] (Table 2). Fifty-six patients (86.6%) had a local recurrence following treatment with the EORTC/NCIC platform and 13.4% manifested a distant noncontiguous recurrence not otherwise defined. An assessment of initial pretreatment pattern of disease or pattern following treatment with BEV was not included nor was survival based on pattern of recurrence.

Iwamoto recently reported on patterns of relapse in 37 adult patients (86% in first relapse) with recurrent GBM treated with BEV (43% with BEV + irinotecan; 38% with BEV + hypofractionated radiotherapy) [9]. The pattern of recurrence prior to BEV based therapy was not reported (Table 2). Following progression on BEV and change of therapy, 13 patients (35%) demonstrated non-enhancing tumor progression, 6 (16%) multifocal disease progression and 17 (46%) local recurrence. Median survival in patients (19/37) receiving salvage therapy after progression on BEV was 5.2 months (0% 6-month progression free survival) compared to the 2.0 median survival in patients receiving no further therapy and supportive care only. The survival in patients treated after BEV progression with alternative therapy in this report is longer than a number of other studies and the present report [2–4, 6]. In part, this difference in survival may be a reflection of patient selection based on pre-treatment with prospective BEV-containing protocols [10]. The difference in survival (5 vs. 3 months) is relevant with respect to trial design in patients failing BEV and being offered investigational therapies.

Lastly and in a report by Silbergeld of 117 adult patients with supratentorial GBM examined postmortem for cause of death, 17% of all patients examined manifested multifocal disease [11]. Notably this report predates the use of both TMZ and BEV and suggests distant invasion is common and expected sequel of treated GBM. The natural history of treated GBM appears then to invade widely irrespective of the administration of anti-angiogenic inhibition. The present study demonstrates that the pattern of diffuse recurrence as defined by Pope is most commonly non-enhancing (>70%). This emergent pattern seen increasingly with the use of anti-angiogenic therapies and discussed in the newly proposed radiographic response criteria for high-grade gliomas, likely reflects relatively non-angiogenic dependent infiltrative and invasive disease unresponsive to angiogenic inhibitors [12]. Furthermore, the natural history of GBM appears to utilize invasion as a paradigm of metastases within the central nervous system and with improvement in survival of patients with GBM, non-local patterns of recurrence are likely to emerge as increasingly common and pose new treatment challenges.

In conclusion, this retrospective analysis suggests a number of radiographic disease patterns are apparent in adult patients with GBM including at diagnosis however the majority are and remain local following recurrence and treatment with BEV. Non-local disease (diffuse, distant or multifocal) is relatively common at all clinically relevant time points (diagnosis and first, second or third recurrence) but does not appear to impact survival or increase in incidence on anti-angiogenic therapy.

Conflict of interest statement The author reports no conflict of interest.

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