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A review of the use of anti-epileptic drugs (AEDs) in high grade gliomas

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Background: Seizures are an important management issue in patients with gliomas. AEDs are often prescribed by neurosurgeons and oncologists. Social implications of having seizures and driving issues need to be addressed. We look at seizure frequency, AED use perioperatively, concomitant medication use and finally documentation of driving recommendations.
Material and Methods: All high grade gliomas diagnosed at a single institution from 2007 to 2008 inclusively were identified. Patients with no histological diagnosis were excluded. Patient medical records and drug charts were reviewed.
Results: Sixty-six patients were included for analysis. 41% (n = 27) were female. The median age was 57.5 years (IQR 45−65). 70%(n = 46) had a diagnosis of gliomblastoma multiforme (GBM), 18%(n = 12) anaplastic astrocytoma (AA) and 12%(n = 8) anaplastic oligodendroglioma (AO). Eight patients (12%) had transformed from a previous low-grade glioma. 39%(n = 26) of patients had radical debulking surgery, 26%(n = 17) had subtotal resections and 33%(n = 23) had biopsy only. 91%(n = 60) received radiotherapy and 83%(n = 55) received temozolomide. Presenting complaint included seizure in 44%(n = 29) of patients. 10.5%(n = 7) developed seizures subsequently. 16%(n = 11) of patients were prescribed prophylactic AED's peri-operatively for a mean duration of 8 days (range 1−17). Prophylactic AED's did not decrease seizure occurrence (p = 0.32). The likelihood of presenting with a seizure was increased by younger age (p = 0.0003), male gender (p = 0.017), WHO tumour grade III (p = 0.0005) and transformation from low-grade glioma (p = 0.001). Thirty-six patients (54.5%) took regular AEDs of which 30% (n = 11) were on combination regimens. Of patients on regular AEDs, 17 patients (47%) had noted drug interactions.
Ten patients (28% of those on AEDs) had ever seen a neurologist and they were more likely to be younger patients (p = 0.0033) and those with a transformed glioma(p < 0.0005). Of these, 60% (n = 6) had regular appointments. Driving recommendations were formally documented in 18% of patients (n = 12). This was more common in those attending a neurology clinic (p = 0.05).
Conclusions: Seizures are a common presentation of high grade glioma. Seizure occurrence after surgery is less common. Concomitant medication poses risk of interactions in this patient population. Review by neurology specialists is infrequent and may be of benefit in the complex area of AED prescribing.

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Salvage therapy with bevacizumab and fotemustine in recurrent high grade gliomas

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Background: Recurrent malignant gliomas (MG) have a poor prognosis with low response rates after salvage chemotherapy. Recent data show that anti-angiogenic therapy is an effective and safe treatment for high grade gliomas recurrent after standard treatment. Bevacizumab (BV) given in combination with irinotecan has been reported to be active with acceptable toxicity. Few data are available on the combination of BV and nitrosoureas, that represents the standard cytotoxic option at recurrence.
Materials and Methods: In this ongoing phase II study patients with MG recurrent after standard treatment (surgery, radiation therapy and concomitant/adjuvant temozolomide) are eligible. Bevacizumab was administered on days 1 and 15 at 10 mg/Kg and Fotemustine (FTM) was administered weekly for 2 consecutive weeks (days 1 and 8) at 75 mg/m^2 (induction phase), followed by a 3 weeks rest period. A maintenance therapy was started in non progressive patients, consisting of BV 10 mg/Kg and FTM 75 mg/m^2 every 3 weeks until progression or unacceptable toxicity. MRI was performed at baseline, at the end of the induction treatment (fifth week) and every 3−4 cycles. Monitoring of CBV with perfusion MRI is performed in selected centers. The co-primary endpoints are objective response rate (ORR), based on Macdonald's criteria (CR+PR) and progression-free survival at 6 months (PFS6), with secondary endpoints of safety, time to tumor progression (TTP) and overall survival.
Results: From April 2008 to April 2009 41 patients (15 females and 26 males), with a median age of 56 yrs (range: 25−69) were enrolled. The overall response rate (CR+PR) was 46% (39% in GBM; 58% in gr.III gliomas). The PFS-6 was 44% (38% in GBM; 48% in gr.III gliomas). The median TTP was of 4 months (range: 1.2−10.3+) (3.3 months in GBM; 5.9 months in gr.III gliomas). The median overall survival was 5.6 months. A significant clinical improvement was seen in 50% of patients, with steroid reduction in 60%. Adverse events were haematological toxicity: grade 1−2 leukopenia in 5 patients, grade 3−4 in 3; grade 1−2 thrombocytopenia in 9 patients, grade 3−4 in 4, 3 intatumoral asymptomatic microhemorrhages, 1 hypertensive encephalopathy and 1 stroke. Others side effects were fatigue (65%), mild hypertension (17%), mild proteinuria (12%), diarrhea (5%).
Conclusions: The combination of BV and FTM is an attractive treatment for recurrent high grade gliomas with acceptable toxicity. The correlations of MGMT status, perfusion MRI and response/outcome are ongoing.

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Improved survival in patients with refractory glioblastoma that response to Irinotecan and Bevacizumab

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Background: Standard therapy of glioblastoma is based on radiotherapy and temozolamide. The majority of these patients show a high incidence of relapse with a median overall survival of 12 months. Previous articles have reported that irinotecan and bevacizumab is an active combination with an acceptable toxicity; however, no enough data are available in the impact of response to bevacizumab on overall survival.
Material and Methods: We retrospectively analized 22 patients with refractory glioblastoma treated with biweekly irinotecan (150 mg/m^2) and bevacizumab (10 mg/kg). Response was assessed following McDonald criteria. Toxicity was recorded according to CTC v3.0 criteria.
Results: Twenty-one patients were assessed. Median age at diagnosis was 46 years. 42.9% of patients had good performance status at the beginning of the treatment (42.9% ECOG 1, 28.6% ECOG 2 and 28.9% ECOG 3). The median of cycles administrated was 4 cycles (2−33). Time to progression in those patients with radiological response was 46 weeks (95% CI: 3.2−88.7) versus 8.5 weeks (95% CI: 8.1−8.8). Overall survival was also longer in those patients with better response to irinotecan-bevacizumab was 44 months from the diagnosis (95% CI: 0.5−82.3). Toxicity grade 3−4 was observed in very few cases: astenia (1 patient) and hypertension (2 patients). The majority of heamotological and non-hematological toxicities observed (87%) were grades 1−2, even in those patients with ECOG 3 in the diagnosis.
Conclusion: Our preliminary data suggests that irinotecan plus bevacizumab is an active regimen with little added toxicity. Patients that showed objective response achieved significant longer overall survival.

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Evaluation of objective response as a predictor of survival in bevacizumab-treated patients with glioblastoma at first or second relapse in the BRAIN Study

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Background: Bevacizumab (BEV), a humanized monoclonal antibody, inhibits the activity of human vascular endothelial growth factor (VEGF). In the BRAIN study (ClinicalTrials.gov number NCT00345163), treatment with BEV alone or in combination with irinotecan demonstrated a clinically meaningful improvement in objective response (OR) rate (28.2% and 37.8%, respectively) in patients with relapsed glioblastoma (GBM) compared to prior studies conducted with other agents in this disease setting. This exploratory analysis was performed to determine if response status was associated with greater residual survival in the BRAIN study.
Materials and Methods: BRAIN was a Phase II, open-label, multicenter, randomized, noncomparative trial of 167 patients, which evaluated efficacy and safety of BEV alone and in combination with irinotecan in patients with relapsed GBM (Cloughesy T et al. JCO;26:2008;2010b). OR rate and 6-month progression-free survival, assessed by an independent review facility, were co-primary endpoints of the study. Pooled data from both treatment arms were used to explore the association of OR with survival.