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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.

Landmark analyses were conducted at 9, 18, and 26 weeks using Cox regression models adjusted for important prognostic factors including age, baseline Karnofsky performance score, first vs. second relapse, and treatment arm. The analysis at each time point required that patients survive until the respective landmark. Hazard ratios for survival between the responder and nonresponder groups were calculated. The goodness of fit, robustness, predictive accuracy, and validation of these models were tested.

Results: There was a statistically significant association between OR and survival. Nonresponders were approximately twice as likely to die compared to responders in a given time period.

	9 Weeks		18 Weeks		26 Weeks	
	Resp	NonResp	Resp	NonResp	Resp	NonResp
N	30	127	46	101	51	72
Hazard Ratio (95% CI)	0.52 (0.32, 0.85)		0.48 (0.31, 0.74)		0.43 (0.27, 0.67)	
P Value (Cox model)	0.0091		0.0010		0.0002	

Resp, Responders; NonResp, Nonresponders.

Conclusions: In the BRAIN study, OR rate was clinically compelling when compared to historical controls. This exploratory landmark analysis with pooled treatment arms suggests that patients with an OR had longer residual survival compared with those who did not have an OR. While these conclusions are limited in the absence of a control arm, OR could be considered a potential predictor of survival in this study of BEV-treated patients with relapsed GBM.

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O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status is a prognostic factor in anaplastic astrocytomas

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Background: *MGMT* methylation status has been found to be an important prognostic factor in glioblastoma patients (pts). However, further data on the epigenetic feature are needed before its role in rare diseases such as anaplastic astrocytomas (AA) can be established.

Methods: A retrospective analysis was made on a database of 139 AA pts followed prospectively from 01/1995 and 08/2008. We evaluated only pts who met the following inclusion criteria: age $\geqslant$18 years; PS 0−2; histological diagnosis of AA; postoperative radiotherapy (RT) and chemotherapy (CT). *MGMT* status was determined with methylation specific PCR. The study aim was to evaluate the role of *MGMT* methylation status in AA. The log-rank test was employed to evaluate the significance of the prognostic variables.

Results: 80 pts (m/f: 46/34, median age: 41 years, range: 18−71 years) were enrolled. *MGMT* was assessable in 71 of 80 pts (88.8%), being methylated in 30 (42.9%) and unmethylated in 41 (57.7%) pts. Median PFS was 48.6 months (95% CI: 33.7−63.5), being 96 months (95% CI: 29−163) and 38 months (95% CI: 18.9−57.2) in *MGMT* methylated and unmethylated pts, respectively ($p = 0.09$). At univariate analysis, complete resection ($p = 0.02$), age ($p = 0.002$), and KPS ($p = 0.003$) were significantly correlated with PFS. At multivariate analysis only age remains correlated with PFS ($p = 0.01$). Median survival (OS) was 93.7 months (95% CI: 63.5−123.8), being not reached and 77 months (95% CI: 20−134.2), in *MGMT* methylated and unmethylated pts, respectively ($p = 0.03$). *MGMT* methylation ($p = 0.03$), age ($p = 0.0003$) and KPS ($p = 0.03$) were significantly correlated with OS at univariate analysis. At multivariate analysis, age ($p = 0.0002$) and *MGMT* methylation ($p = 0.01$) were correlated with a better OS.

Conclusions: *MGMT* methylation status is an independent prognostic factor together with age in AA. This datum should provide the background to improve the therapeutic index with temozolomide concurrent with and adjuvant to RT in AA.

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MGMT methylation status does not provide adjunctive prognostic information in pts with 1p/19q intact anaplastic gliomas

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Background: Chromosomes 1p/19q codeletion has been recognized as a prognostic and predictive factor in patients (pts) with anaplastic gliomas (AG). Non-codeleted (intact) anaplastic oligodendroglioma showed a survival comparable to that usually observed in pts with anaplastic astrocytomas; *MGMT* methylation status, moreover, has been found to be a prognostic factor in glioblastoma and anaplastic gliomas.

Methods: A retrospective analysis was made using a database of 253 AG pts followed prospectively between 01/1998 and 11/2008. We evaluated only pts who met the following inclusion criteria: age $\geqslant$18 years; PS 0−2; histological diagnosis of AG with 1p/19q intact, as determined by FISH analysis; treatment with postoperative radiotherapy (RT) and chemotherapy (CT); *MGMT* status determined using methylation specific PCR. The study aim was to evaluate the role of *MGMT* methylation status in 1p/19q codeleted AG pts. The log-rank test was used to evaluate the significance of the prognostic variables.

Results: 75 pts (m/f: 39/36, median age: 40 years, range: 18−70 years) were enrolled. Histology was anaplastic oligodendroglioma in 19 pts, anaplastic oligoastrocytoma in 22 pts and anaplastic astrocytoma in 34 pts; all these pts were 1p19q intact and received surgery, RT and CT. *MGMT* status, assessable in 66 pts (88%), was methylated in 38 pts (57.6%) and unmethylated in 37 pts (49.3%). Median progression-free survival (PFS) was 27 months (95% CI: 13.1−40.9). In multivariate analysis, no enhancement at time of diagnosis ($p = 0.03$) and gross total resection ($p = 0.04$) were significantly correlated with better PFS. Median survival was 74 months (95% CI: 55.9−92.1). In multivariate analysis, only age ($p = 0.005$) and KPS ($p = 0.045$) correlated with a better survival.

Conclusions: *MGMT* methylation status does not seem to provide adjunctive prognostic information in pts with 1p/19q intact AG.

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Immunological assessment of IL-2 effectiveness in chemotherapy in children with medulloblastoma

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The goal is to assess IL-2 immunological effectiveness during chemotherapy in children with medulloblastoma.

Patients and Methods: During induction chemotherapy, which included 4 cycles with vincristin, etoposid, cyclophosphamid, cisplatin or carboplatin, recombinant yeast interleukin-2 (Roncoleukin) was used based on the blind randomization method. Patients were divided into two groups depending on the presence of cytokine therapy in their treatment scheme: patients of the first group (I) received Roncoleukin the day before and during all 3 days of the induction chemotherapy (21 patients). The agent was given intravenously, in dose 1 million IU/m^2 during each chemotherapy cycle. Patients of the second group (II) did not receive biotherapy (21 patients). To assess Roncoleukin clinical effects, infectious complications were noted after each chemotherapy cycle and estimated according to CTC (Common Toxicity Criteria, NCI, Version 3.0, 2003). To assess Roncoleukin immunomodulating effect, lymphocyte subpopulation, T-lymphocyte activating markers expression and circulating cytokines level were investigated.

Results: The usage of IL-2 results in stable content of T-lymphocyte and its subpopulations during all chemotherapy cycles, whereas during chemotherapy without IL-2 substantial change in CD4+/CD8+ lymphocytes with the prevalence of CD8+ cells, as well as the increase of total portion of CD3+ lymphocytes and significant decrease of B-lymphocyte portion ($p < 0.05$) are observed. In the investigated groups, substantial increase of the portion of activated T-lymphocytes (CD3+HLA-DR+) occurs and more apparent changes are seen in the group of patients, that has not received IL-2 ($p < 0.05$). This tendency has also its effect on the inflammatory cytokine levels of TNF and IL-6. The portion of T-helpers expressing receptors for IL-2, relatively to the total T-helpers account, is characterized by its higher level in the group that received IL-2. At the beginning of IL-2 use, the quantity of infectious complications practically did not differ in both groups. By the fourth polychemotherapy cycle, infectious complications were lower more than by 3 times in the group of patients that received IL-2, than in the one without immunotherapy ($p < 0.05$).