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Bevacizumab and Fotemustine for Recurrent Glioblastoma − Final Results of a Multicenter Phase II Study of AINO (Italian Association of Neuro-Oncology)

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Background: Bevacizumab (BV) has shown activity in recurrent glioblastoma (GBM), both alone and in association with chemotherapeutic agents. Few data are available on the combination of bevacizumab and nitrosoureas, that represent the standard cytotoxic option at recurrence. Fotemustine (FTM) is a nitrosourea with elevated lipophilic properties, and demonstrated activity in recurrent GMBs as single agent.
Methods: In this phase II study patients with GBM recurrent after surgery, radiation therapy, and concomitant/adjuvant temozolomide were elegible. The treatment consisted of an induction phase with BV at 10 mg/kg intravenously on day 1 and 15 and fotemustine (FTM) at 75 mg/m^2 intravenously on day 1 and 8, followed after 3 week interval by a maintenance phase with BV at 10 mg/kg i.v. and FTM 75 mg/ m^2 every 3 weeks until tumour progression or unacceptable toxicity. Patients had undergone clinical and MRI assessment 1 month after the start of treatment and thereafter every 2 months. The primary endpoint was progression-free survival at 6 months (PFS6), whereas secondary endpoints were response rate (RR), based on RANO criteria, progression-free (PFS) and overall survival (OS), and safety.
Results: From April 2008 until November 2010, 54 patients (males 35, females 19, median age 57) were enrolled. PFS6, PFS12 and mPFS were 44%, 21% and 5.29 months respectively. mOS was 9.13 months with 77.4% and 31% of patients surviving at 6 and 12 months respectively. Response rates were as follows: 2CR (4%), 24 PR (44%), 22 SD (41%) and 6 PD (11%). A significant neurological improvement was observed in 57% of patients, being steroids reduced or interrupted in 64%. 44/54 (81%) patients have progressed and patterns of progression were local in 29/44 (66%), multicentric 10/44 (23%), gliomatosis 3/44 (6%) and isolated leptomeningeal spread 2/44 (5%). 12/54 (22%) patients with grade III/IV piastrinopenia/leukopenia discontinued fotemustine, whereas 4/54 (7.4%)discontinued bevacizumab (1 stroke, 1 intratumoral haemorrhage, 1 GI perforation and 1 pulmonary embolism.
Conclusions: Combination of bevacizumab and fotemustine in glioblastomas recurrent after standard radiotherapy + temozolomide is safe and promising. The analysis of MGMT methylation status is ongoing.

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SOX8 as a Molecular Marker of Oligodendroglial Tumours

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Background: The precise diagnosis of oligodendroglial tumours from astrocytic tumours is required because the sensitivity to conventional treatments including chemotherapy and irradiation is different between these two types of gliomas. However, morphological diagnosis of these tumours is not always easy and diagnosis is sometimes different among pathologists. Recently, *SOX8* has been reported to be involved in the development of oligodendrocyte. The aim of this study is to clarify the clinical significance of *SOX8* expression as a molecular diagnostic marker of oligodendroglial tumours.
Materials and Methods: 74 gliomas (OII: 7, OIII: 15, AIII: 5, GBM: 47) were enrolled in this study. The expression level of *SOX8* was evaluated by real-time PCR in all cases. Array CGH was also performed in all cases and 1p/19q deletion was defined as co-deletions of whole arms of 1p and 19q. Among these cases, *MGMT* promoter methylation status was also evaluated in 44 tumours by methylation-specific PCR. The difference in expression levels of *SOX8* owing to the morphological diagnosis and 1p/19q status were evaluated. Furthermore, the survivals of patients were compared between the tumours with high (>3000) and low expressions ($\leqslant$3000) of *SOX8* in order to evaluate the significance of *SOX8* as prognostic factor of gliomas.
Results: The expression level of *SOX8* was significantly higher in oligodendroglial tumours than astrocytic tumours (median: 8801 vs. 578, $p < 0.0001$). High-expression of *SOX8* was also demonstrated in 1p/19q deleted tumours in compared with those without 1p/19q losses (8865 vs. 619, $p < 0.0001$). The frequency of *MGMT* promoter methylation was higher in tumours with high SOX8 expression than those with low expression of *SOX8* (80% vs. 56%), although statistical significance was not proven. In oligodendroglial tumours, the survival of patients with tumours of high *SOX8* expression was significantly better than those with low *SOX8* expression (median: 10.8 vs. 2.5 years, hazard ration: 6.5, $p = 0.014$). This tendency was also observed in astrocytic tumours, and patients with high SOX8 GBMs showed better survival (1.5 years) than those with low *SOX8* (1.3 years), although this difference was not significant ($p = 0.335$).
Conclusions: *SOX8* was highly expressed in 1p/19q deleted oligodendroglial tumours. In oligodendroglial tumours, the expression of *SOX8* was the significant prognostic factor of patients' survival.

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Neurocognitive Function (NCF) Impairment Following Fractionated Stereotactic Radiotherapy (FSRT) for Benign or Low-Grade Adult Brain Tumours

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Purpose/Objective: To prospectively evaluate the association between dose to the hippocampus and long-term NCF impairment for benign or low-grade adult brain tumours treated with Fractionated Stereotactic Radiotherapy (FSRT) using optical guidance.
Materials and Methods: Adult Patients with low-grade glioma, meningioma, pituitary adenoma or vestibular schwannoma, were enrolled on our prospective trial and treated with FSRT. No attempt was made to spare the hippocampus. Language, visual perception, processing speed, memory, executive function, and intelligence were assessed at baseline and at 18 months follow-up. Regression-based standardized Z-scores were calculated using 6 similar healthy controls evaluated at the same test-retest interval, with covariate factors of age, years of education, and gender. NCF impairment was defined as Z score $\leqslant -1.5$. The hippocampus was delineated using RTOG 0933 guidelines, and dose-volume histograms were generated for the left and right hippocampus and for the whole hippocampus. Equivalent doses in 2-Gy fractions (EQD_2) assuming $\alpha/\beta = 2$ were computed. 1-tailed Fisher's exact test was used to compare NCF impairment with each hippocampal dosimetric parameter, dichotomized around the median. Binary logistic regression was used in multivariate analysis with age as a categorical covariate ($\leqslant$50 vs. >50).
Results: 18 patients, including 9 with vestibular schwannoma, 4 with low grade glioma, 3 with meningioma, and 2 with pituitary adenoma, were enrolled in this prospective trial and have remained recurrence-free at 18 months follow up. Univariate statistical analysis demonstrated associations between impairment in

a. Wechsler Memory Scale-III Word Lists Delayed Recall (WMS-WL-DR) and EQD_2 >7.3 Gy to 40% of the hippocampus ($p = 0.025$);
b. WMS-WL-DR and EQD_2 to 100% of the hippocampus >0 Gy ($p = 0.047$);
c. Hooper Visual Organization Test (HVOT) and maximum-EQD_2 to the left hippocampus larger than 15.0 Gy ($p = 0.041$); and,
d. HVOT and EQD_2 >6.2 Gy to 30% of the left hippocampus ($p = 0.041$).

On multivariate statistical analysis, the association between

a. WMS-WL-DR impairment and EQD_2 >7.3 Gy to 40% of the hippocampus remained significant (Odds Ratio (OR) 19.3, $p = 0.043$);
b. WMS-WL-DR impairment and EQD_2 to 100% of the hippocampus >0.0 Gy trended to significance (OR 14.8, $p = 0.068$); while,
c. HVOT and maximum EQD_2 to the left hippocampus as well as HVOT and EQD_2 to 30% of the left hippocampus lost statistical significance.

Conclusions: An EQD_2 to 40% of the hippocampus greater than 7.3 Gy is associated with long-term impairment in list-learning delayed recall following FSRT for benign or low-grade adult brain tumours.