

planning and preparation for treatment, and eligibility and entry for clinical trials and consent. Patients are offered as many appointments as they require. **DISCUSSION:** Patients with brain tumors are being offered increasing options for treatment; however, the trauma of the diagnosis and the complexity of the discipline call for much greater communication with and planning from the treatment team. We have implemented a novel PTAC run primarily by nonmedical staff as an efficient and effective mechanism to respond to these demands. We plan to audit measures of effectiveness and satisfaction during the change-over period to demonstrate its value.

P.101. MALIGNANT GLIOMA SURGERY IN ELOQUENT BRAIN AREAS

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OBJECTIVES: The surgical studies have demonstrated that the extent of anaplastic glioma resection is significantly correlated with patient median survival. Removal of brain tumors adjacent to eloquent areas remains a procedure with high-level postoperative neurological disorders as a result of wide tumor infiltration of functional cortex and subcortical pathways. Accurate preoperative and intraoperative identification of the eloquent cortex is an essential adjunct to successful surgical excision of gliomas involving motor and speech area. **METHODS:** A total of 36 patients (21 males, 15 females, mean age 48.3 years, range 21–70 years) who underwent resection of cortical or subcortical tumors located within or close to motor areas have been included in the series. The preoperative planning was done by integrating CT, MRI, fMRI, SPECT, and computed EEG studies. Brain tumors located in eloquent area in 21 patients (motor area in 12 cases, sensory area in 9 cases) and in close to eloquent area in 15 patients (motor area in 8 cases, sensory area in 7 cases). Tumor microsurgery resection was carried out using the StealthStation navigation system accompanied with intraoperative laser thermodestruction (808 nm, 18 W). **RESULTS:** Sixteen patients had glioblastoma multiforme and 20 had anaplastic astrocytoma. A gross total or nearly gross total tumor resection was accomplished in 19 patients, and subtotal resection was carried out in 17 patients. Neuronavigation technology helped to define the radiographic limits of the tumor, to perform preoperative planning and minimal access craniotomy. The intraoperative orientation by connection of anatomical and functional landmarks allowed performing image-guided tumor excision beyond functional zones with maximal extension of tumor resection volume. Laser thermodestruction of residual tumor parts was used after microsurgical tumor removal in regions around sensorimotor and speech areas. Laser thermodestruction increased the rate of complete citoreduction and performed an aimed coagulation without traumatization of eloquent cortex. **CONCLUSIONS:** The gross total resections of anaplastic gliomas could be performed in eloquent brain regions with an acceptable level of motor and speech impairment. The improved preoperative functional mapping, intraoperative neuronavigation techniques with laser thermodestruction allow maximal safe resection of tumor that predict higher levels of quality of life in patients with brain gliomas in eloquent area.

P.102. NEAR-CONTINUOUS TEMOZOLOMIDE AND LOW-DOSE WEEKLY CCNU: A NOVEL CHEMOTHERAPY REGIMEN WITH ACTIVITY IN MALIGNANT GLIOMAS RESISTANT TO DOSE-DENSE TEMOZOLOMIDE ALONE

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BACKGROUND: Alkylating chemotherapy with CCNU is active in recurrent malignant glioma, but may be antagonized by anti-alkylating MGMT. Here, we present feasibility and activity of a novel regimen aiming at depletion of MGMT with lower dose, near-continuous temozolomide followed by low-dose weekly CCNU to treat recurrent malignant gliomas resistant to dose-dense temozolomide. **METHODS:** Eleven consecutive patients with recurrent malignant gliomas (4 glioblastomas, 3 gliosarcomas, and 4 anaplastic gliomas) were treated: 6 males (55%), 5 females (45%); mean age at first diagnosis was 55.9 (19–76) years; median Karnofsky Performance Status 70%; 9 patients were treated for a second recurrence and 2 for first recurrence. All patients were pretreated with dose-dense temozolomide (day 1–21/28 or 1–5/7, initial dose 100 mg/m²). Nine of the 11 patients were switched without delay from dose-dense temozolomide monotherapy to combined near-continuous temozolomide (50–60 mg/m² day 1 5/7) plus weekly low-dose CCNU (40 mg fix dose at day 6/7). **RESULTS:** In total, 32 cycles of chemotherapy were applied. The combination was well tolerated in terms of nausea and fatigue. Blood counts decreased

continuously, enabling a gradual dose adaptation. Hematological WHO grade III + IV toxicity occurred in 5 of 11 patients (45%), 2 of them were symptomatic. One patient had a prolonged elevation of liver enzymes which improved partially after termination of levetiracetam. Best responses after ≥2 months were: 1 complete and 2 partial remissions (27%), 3 stable diseases (27%), 5 progressive diseases (46%). Median overall survival after start of chemotherapy was 4.5 months, progression-free survival at 6 months (PFS 6) was 18%, and overall survival from first diagnosis 23.5 months. **CONCLUSIONS:** In spite of adverse prognostic signs, the objective remissions indicate activity of combined near-continuous temozolomide and low-dose weekly CCNU after failure of dose-dense temozolomide alone. Hematotoxicity, though, has to be controlled vigorously. The results have to be controlled in a larger, prospective series.

P.103. RADIOTHERAPY PLUS CONCOMITANT AND ADJUVANT TEMOZOLOMIDE FOR GLIOBLASTOMA IN ELDERLY PATIENTS

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OBJECTIVES: The optimal treatment for elderly patient with glioblastoma remains controversial. The aim of this study was to verify the activity and the toxicity of temozolomide (TMZ) administration concurrent and adjuvant to radiotherapy in elderly patients with glioblastoma (GBM), and to explore correlation between clinical outcome and O(6)-methylguanine-DNA-methyltransferase (MGMT) promoter methylation status. **PATIENTS AND METHODS:** From April 2006, 25 consecutive newly diagnosed GBM patients aged 65 years or more (median age 72 years) and a KPS of >50 were treated with radiotherapy (total of 60 Gy for 18 patients and 40 Gy for 7 patients) plus continuous daily TMZ (75 mg/m²/day), followed by maintenance TMZ cycles (200 mg/m² once a day for 5 consecutive days ever 28 days) until complete response or unequivocal progression. **RESULTS:** The median OS was 13.7 months and median PFS was 8.3 months. The 6- and 12-month survival rates were 79% and 61%, respectively. The 6- and 12-month PFS rates were 54% and 40%, respectively. Four patients had grade III neutropenia and 1 patient had grade III thrombocytopenia and 11 patients had grade III/IV lymphocytopenia. Two patients had grade III infection resolved with medical therapy. Leukoencephalopathy was diagnosed in 2 patients who survived more than 12 months. This was associated with memory loss in 1 patient. The methylation status of the MGMT promoter was evaluated in 23 patient samples. The median OS was 25.8 months vs 9.0 months in patients with MGMT promoter methylated status and with unmethylated MGMT promoter status, respectively ($P = .05$). **CONCLUSIONS:** Radiotherapy plus concomitant and adjuvant TMZ was well tolerated with an acceptable rate of toxicity, and patients with a MGMT promoter methylated status had a better survival. However, further prospective trials are needed to confirm these results.

P.104. SAFETY ANALYSIS OF RANDOMIZED BELGIAN PHASE II TRIAL OF EXTENDED USE OF ADJUVANT TEMOZOLOMIDE IN NEWLY DIAGNOSED GLIOBLASTOMA PATIENTS

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PURPOSE: We conduct a Belgian randomized phase II trial to determine whether prolonged administration of temozolomide (TMZ) in newly diagnosed GBM patients increases their progression-free survival (PFS). We also assess the safety profile of this extended use of TMZ since no data are available yet. **METHODS:** Patients with newly diagnosed glioblastoma presenting with a response or stable disease after the standard treatment of 6 months adjuvant TMZ, were included. These patients were randomized between continued treatment with TMZ or observation, using residual tumor and MGMT status as stratification factors. Patients randomized in the observation arm were rechallenged with TMZ upon progression. We will report here the PFS at 6 months and the safety analysis from the interim analysis. **RESULTS:** The first 20 patients included were comparable between both arms in terms of the well-known prognostic factors such as median age at diagnosis 55 vs 56 years, Karnofsky score 84 vs 92%, residual tumor in 8 vs 9 patients, and steroids use for 5 vs 2 patients in prolonged TMZ arm and observation arm, respectively. The progression-free survival (PFS) at 6 months was 70% vs 57%, respectively. The median number of cycles was 6 in the prolonged TMZ arm. Three patients presented with a complete response after 6 months of added TMZ. The mean number of all

grade toxicity per patient was $3.5 (\pm 3.3)$. The toxicities of TMZ were, in the majority of cases, limited to grade 1–2; 4 patients had an asymptomatic grade 3 lymphopenia, 3 had grade 3 asymptomatic thrombopenia, and 1 patient had a grade 4 lymphopenia. But only 1 patient out of the 10 included in this arm had to stop TMZ because of hematological toxicity. In the observation arm, 5 patients were rechallenged and 3 cycles were given without any response. Patients presented with grade 1 toxicity and only 1 patient had a grade 2 lymphopenia. **CONCLUSION:** Hematotoxicities are more frequent in the prolonged adjuvant TMZ arm but only 1 patient had to stop treatment. This analysis shows a potential benefit of the experimental arm in terms of PFS at 6 months. Accrual is nearly completed and updated results on safety will be reported.

P.105. VAULTS AND THE MAJOR VAULT PROTEIN (MVP): IMPACT ON THE MALIGNANT PHENOTYPE OF HUMAN GLIOBLASTOMA MULTIFORME

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Vaults are highly conserved ribonucleoprotein particles containing a small untranslated RNA (vRNA). The 110-kDa major vault protein (MVP) has been implicated in the regulation of multiple cellular processes, including transport mechanisms, chemoresistance, and several signaling cascades/molecules (eg, MAPK and PI3K pathway). While in normal brain the expression of MVP is very low, MVP expression is consistently upregulated in gliomas including glioblastoma multiforme (GBM). Aim of this study was to investigate whether MVP/vaults have an impact on GBM cell growth and aggressiveness, including chemotherapy responsiveness and to clarify underlying molecular mechanisms. MVP and MVP-GFP fusion proteins were overexpressed by plasmids and adenoviral constructs. Endogenous MVP expression was repressed by shRNA. Protein expressions were detected by immunofluorescence and Western blot. Consequences of MVP modulation on cell proliferation, migration, and invasion capacities were analyzed by growth curves, scratch and transwell-chamber assay, respectively. Moreover, tumor formation in dependence of MVP expression was tested in SCID mice. Ectopic MVP expression in MVP-negative H7 glioma cells led to a significantly enhanced proliferative and migratory potential in vitro. Especially responsiveness to epidermal growth factor (EGF)-mediated growth stimulation was increased paralleled by significant upregulation of MAPK and PI3K pathway indicated by phosphorylation of ERK and AKT, respectively. Accordingly, several signal mediators of these pathways, including PTEN and pS6, were detected in immunoprecipitates from MVP-overexpressing cell clones. MVP transgenic cells were significantly resistant to cell death induced by serum-starvation but only marginally protected against the cytotoxic effects of diverse chemotherapeutics. Expression of a truncated MVP molecule harboring only the MVP coil-coiled domain and/or MVP downmodulation by shRNA in MVP-positive GBM cells induced programmed cell death as well as hypersensitivity to growth factor starvation. Tumor growth in SCID mice was significantly enhanced in all MVP overexpressing H7 subclones when compared with vector controls. Our data proof a significant contribution of vaults/MVP to the malignant phenotype of human GBM cells by supporting activation of oncogenic signaling pathways and growth/survival factor responsiveness.

P.106. A FIVE-YEAR FOLLOW-UP EXPERIENCE IN NEWLY DIAGNOSED GLIOBLASTOMA AND CONCOMITANT PROTOCOL: TOLERANCE, COMPLIANCE, EFFECTIVENESS, AND SECOND-LINE THERAPIES

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Since 2005 the Stupp protocol with concomitant regimen of chemoradiotherapy followed by monthly adjuvant cycles of temozolomide has become the standard first-line approach in newly diagnosed glioblastoma after surgery. In this study, we present a 5-year follow-up experience in newly diagnosed glioblastoma treated with the concomitant protocol at the Neurosurgery Units of Policlinico and Galeazzi Institutes. From January 2005 to December 2009, we enrolled 91 patients eligible to complete the concomitant phase. We excluded patients in poor general or neurological conditions who needed a rehabilitation period prior to be submitted to

radiotherapy. People over 70 years old were addressed to a modified protocol with a reduced dosage of radiotherapy, except for 3 patients in very excellent conditions who were submitted to standard protocol. There were 38 women and 53 men ranging from 18 to 75 years. All of them were submitted to gross total removal of the lesion (as assessed by postoperative gadolinium-enhanced CT or MRI scan) except for 6 deep-seated lesions, submitted to stereotactic biopsy. In 63 cases, MGMT status was analyzed. All the patients were able to finish the concomitant phase of the protocol. In 4 cases, a reduced dose of temozolomide was administered because of the onset of pias-trinopenia. In the adjuvant phase, we preferred to administer 12 monthly cycles of temozolomide instead of the standard 6 months regimen. In the majority of patients (90%), we adopted a modified schedule (150 mg/day 1–5 day, 75 mg/day 6–10 day). Four patients experienced a bronchopneumonia, 2 during the concomitant phase, and 2 during the adjuvant phase. At 6 months 100% of patients were alive, at 12 months 75% of patients, at 24 months 22%, and at 36 months 10%. Median survival was 15 months and median time tumor progression was 12 months. Twelve patients had second surgery at recurrence (in 9 of them Gliadel wafers were placed in the cavity), and 80% of the patients with recurrence received a second-line therapy: rechallenge of temozolomide (the 1-week on–one week off regimen in unmethylated tumors), fotemustine, bevacizumab. We also analyzed the quality of life of the patients, the clinical (Karnofsky score) and neuropsychologic status (MMSE), the duration of hospital stay, and days spent in outpatients' visits. Finally, we concluded that a good tolerance of the concomitant regimen was observed in the majority of patients, determining an acceptable quality of life and, thus, an improved access to second-line therapies.

P.108. UPDATED RESULTS OF A PHASE II TRIAL OF BEVACIZUMAB AND IRINOTECAN IN RELAPSED HIGH-GRADE GLIOMA

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BACKGROUND: Relapsed glioblastoma multiforme (GBM) has a poor response to current chemotherapy and prognosis of patients with recurrent disease is dismal, with a median survival of 3–6 months. Numerical trials using bevacizumab, a humanized IgG1 monoclonal antibody to vascular endothelial growth factor (VEGF), with or without chemotherapy, have reported excellent response rates using 10 mg/kg or 15 mg/kg every 2 weeks, and allowed expedite FDA approval for its use as a second-line treatment in relapsed GBM. We performed a phase II trial of bevacizumab using 5 mg/kg only, with irinotecan (CPT 11) every 2 weeks as reported in the initial presentation by Stark Vance. In our interim analysis, we had demonstrated excellent response rates and similar results to others. This is an update of the final results. **PATIENTS AND METHODS:** This phase II trial accrued 30 patients with recurrent GBM who received bevacizumab at 5 mg/kg and CPT 11 at 125 mg/m² every 2 weeks, after failing radiation therapy and adjuvant TMZ. All patients on antiepileptic drugs (AEDs) had their regimen changed to nonenzyme-inducing antiepileptic drugs (NEIAEDs) prior to receiving CPT 11. Patients with KPS $\geq 50\%$ were allowed regardless of prior relapses. Patients were evaluated clinically and with contrast-enhanced MRI scan every 4 treatments of bevacizumab until progression. **RESULTS:** All 30 patients were evaluable. Responses were assessed radiographically according to the MacDonald criteria and comparing T2 or Flair weighed Sequences; 19 patients (63%) had a documented response (CR + PR), 6 patients (20%) had stable disease (SD) and 5 patients (19%) progressed (PD). The average number of bevacizumab treatments received was 5.6 (1–20). The 6-month progression-free survival was 33.4%; 6-month overall survival was 66.7%, median overall survival was 8.7 months (36.3 weeks); median progression-free survival was 5 months (22.8 weeks). Several complications were reported: 3 DVTs and 2 PEs requiring IVC filter placement, 2 intracranial hemorrhages and one nonneurosurgical complication. All patients had a clinical benefit and were taken off steroids rapidly after starting bevacizumab regardless of radiological response. Clinical and radiographic responses correlated well. Failures were mostly local progression in 12 cases, infiltrative nonenhancing (gliomatosis like) in 10 cases and multifocal including subependymal and leptomeningeal in 8 patients. **CONCLUSION:** Bevacizumab-based regimen for relapsed GBM demonstrates superior activity when compared with historical treatments. It is safe and improves overall quality of life in this patients' category. Our results were as attractive as previously reported series despite lower KPS on enrollment, and using lower doses of bevacizumab.