METHODS: A systematic search of electronic databases (PubMed, EMBASE, OVID, Web of Science, The Cochrane Library) were performed to identify related studies published from 1970 to 2013. RCTs comparing BV with ST for newly diagnosed HGG were included. The quality of the included trials was assessed and the RevMan 5.1 software was applied to conduct meta-analysis.

RESULTS: Seven RCTs with a total of 2122 patients were included. The median progesterone-free survival (PFS) in the BV group was higher than that in the ST group (pooled hazard ratio 0.86, 95% CI 0.75–1.0, p=0.004). We also found high PFS rate in BV group at 6 month (OR 3.29, 95% CI 2.64–4.18, p<0.00001), and 12 month (OR 2.06, 95% CI 1.71–2.49, p<0.00001), compared with ST. No significant differences were observed between BV and ST groups in median overall survival. For the incidence of adverse events, three adverse outcomes were found to be significantly different between BV and ST groups, including hypertension (8.37% vs. 1.62%, p<0.00001), proteinuria (1.75% vs. 0.0%, p=0.001), and fatigue (14.54% vs. 9.01%, p=0.001).

CONCLUSION: This study indicated that combination of BV with ST for newly diagnosed HGG did not improve the median overall survival but result in longer median PFS, maintaining the quality of life and functional status. However, the result gave rise to the increasing of adverse event incidence and neurocognitive decline rate. Further clinical trials were needed to assess the long-term functional outcomes of BV in newly diagnosed HGG.

P008.03 ERUCIC ACID, A COMPONENT OF LORENZO’S OIL USED IN TREATMENT OF ADRENOLEUKODYSTrophy, ACtS ANTeINOPLASTIC IN C6 GLIOMA CELL CULTURE

M. A. Altinoz1, A. Bildir2, E. H. Bolukbasi1, R. Sarti3, Z. Yazici3, I. Elmaci1

1Dept of Neurosurgery, Memorial Hospital, Istanbul, Turkey, 2Dept of Histology and Embryology, Zirve Universities, Gaziantep, Turkey, 3Dept of Pharmacology, Cerrahpasa Faculty of Medicine, Istanbul, Turkey.

INTRODUCTIONS: Adrenoleukodystrophy (ALD) is a disease caused by the accumulation of very long chain fatty acids in adrenal and cerebral tissues. For the treatment of ALD, a mixture of ω-3 fatty acids (olive and canola) is being used. Erucic acid (EA) also significantly exists in the Asian diet. At first, the safety of EA was largely debated partly due to the Spanish Toxic Oil Syndrome (STOS), when severe cardiomyopathy was observed among consumers of rapeseed oils rich in EA. It was proposed that this is high toxic to cardiac mitochondria. But several studies showed that STOS cases were only seen among consumers of rapeseed oils, which were refined with carcinogenic aniline dyes. Furthermore, opponents of mitochondrial toxicity theory have applied EA at unapplicable doses. Since EA also binds transcription factor PPAR-delta capable to induce oligoden-droglial differentiation of glial progenitors, we aimed to define EA effects on C6 glioma growth in vitro. PPARs also involve in induction of nitric oxide synthases (NOS) and in mitochondrial-proliferation. We also studied in vivo interactions of EA with the toxicity of doxorubicin (Dox) which is a chemotherapy drug used for treatment of primary CNS tumors. For the treatment of neurocognitive decline rate, the contribution of PI3-Kinase pathway on the anti-invasive efficacies and grade in gial neoplasms. Progestosterone gradually increases from the first until the last day of pregnancy and reaches 200-fold of its prepartum levels. Glial tumors manifest more during the first trimester yet their incidence becomes lesser in the last trimester of gestation. Additionally, in contrast to meningiomas, women gender, being everaparous and proges-
terone-containing hormone replacement therapy (HRT) reduces risk of gial tumors. Medroxyprogesterone acetate (MPA) is a widely used 17-OH-pro-
gestosterone which is used in HRT and strongly binds to a progesterone receptor and to a lesser extent, glucocorticoid receptor (GR). Antiedema agents like dexamethasone (Dex) bind to the GR, which were also shown to reduce glial tumor invasiveness.

MATERIALS AND METHODS: In this investigation, we studied in vitro antitumor effects of MPA on human glial tumor cell lines (U87 and U251) and the contribution of PI3-Kinase pathway on the anti-invasive efficacies of MPA and Dex. We also studied in vivo efficacy of MPA on C6 glioma implanted into Wistar rat brains.

RESULTS: At low doses (3.25 to 16.3 μM) MPA slightly and insignificantly induced growth of U87 and U251 human glialblastoma cells in monolayer cultures. At doses higher than 52 μM, cell numbers drastically reduced and few cells survived at 104 μM. In 3D-spheroids cultures maintained in semisolid type-I collagen, MPA and Dex dose-dependently reduced tumor invasion even at low dosages. Unexpectedly, PI3-Kinase inhibitors LY294002 and wortmannin at low dosages hindered antitumor effects of both MPA and Dex, PI3-Kinase pathway is mostly pro-tumorigenic; yet few studies also demonstrated that this pathway may also transmit antitumor signals. To the best of our knowledge, this is the first study which showed that benefits of antiedema steroids in glial tumors may occur via PI3Kinase. In Wistar rats inoculated with C6 glioma, 50 mg/kg/day MPA reduced tumor volume by about 50 percent in 3 weeks.

CONCLUSIONS: Considering the high safety of MPA and also that blood progesterone levels up to 160 μM are tolerable in human, these current investigations warrant further study.

P008.05 COMBINED PRESENCE OF THREE MGMT GENE POlyMorphisms IN A Glioblastoma PATIENT, WHO DEVELOPED SEVERE MYELOsuppression FOLLOWING TEMozolomide CHEMOTHERAPY

M. A. Altinoz1, E. Ozek1, C. G. Ekmekci2, G. Yenmis3, I. Elmaci1

1Dept of Neurosurgery, Memorial Hospital, Istanbul, Turkey, 2Dept of Genetics, Acibadem University, Istanbul, Turkey.

INTRODUCTION: Temozolomide chemotherapy can cause thrombocyto-
openia or neutropenia in 3 and 4 percent of patients, respectively; however pancytopenia cases were very rarely reported. MGMT (O6-methylguanine-
DNA-methyltransferase) enzyme repairs temozolomide-induced guanine base mutations in the DNA and it is important both for the tumor response and toxic/myelotoxic side effects in glioblastoma patients. DNA repair mech-
isms (both MGMT and DNA-PKcs) are related with general myelotoxicity of temozol-
omide. Another study have reported rs12917 variant of the MGMT-gene in two patients with temozolomide-induced severe myelosuppression.

MATERIALS AND METHODS: We performed full-sequencing of the MGMT gene (via Applied Biosystems Biosequencing®) in a female glioblas-
toma patient, who developed pancytopenia and sepsis following temozolomide treatment.

RESULTS: We have encountered that this patient carried all the rs2308321, rs2308327 and rs12917 variants of the MGMT-gene associated with temozolomide myelotoxicity. Interestingly, rs12917 variant was previ-
ously reported to associate with lesser risks of gallbladder cancer and gial tumors and with higher risk of non-Hodgkin lymphomas following expo-
sure to organic chlorinated solvents or hair-dyes and, hence, the same variants of the same DNA repair genes may differentially influence cytotoxic or tumorigenic DNA damage. Until recently, only one case-series study exists which showed that rs2308321 and rs2308327 variants of the MGMT-gene is associated with temozolomide myelotoxicity.

CONCLUSIONS: The sum effect of multiple rare variants and/or coexposure to multiple environmental mutagens may have triggered glioblas-
toma formation and myelotoxicity in this patient. In future, routine full-
sequencing of MGMT gene may help to predict patients with high risk of temozolomide-toxicity.

P008.06 TRANSCRIPTIONAL CHANGES INDUCED BY BEvacizumab COMBINATION THERAPY IN RESPONDING AND NON-RESPONDING RECURRENT Glioblastoma PATIENTS

T. Urpu1, L. Staunstrup2, S. Michaelisen1, K. Vitting-Serup3, M. Bennedsen4, A. Tofti5, H. Broholm6, P. Hamerlik4, H. Poulsen1, E. Jensen1

1Department of Radiation Biology, The Finsen Center, Copenhagen University Hospital, Copenhagen, Denmark, 2Section for Computational and RNA Biology (SCARB), Department of Biology, University of Copenhagen, Copenhagen, Denmark, 3Center for Genomic Medicine,
BACKGROUND: Bevacizumab combined with chemotherapy is among the most frequently used treatments in recurrent glioblastoma, and patients who achieve response to bevacizumab have improved survival as well as quality of life. The aim of this study was to investigate transcriptional changes associated with in vivo response and resistance to bevacizumab therapy.

MATERIAL AND METHODS: The study included 21 recurrent glioblastoma patients who were response evaluable and had biomarker assessable tumor tissue surgically removed both before bevacizumab treatment and at time of progression. Patients were grouped into responders (n = 7) and non-responders (n = 14). Gene expression profiling of formalin-fixed paraffin-embedded tumor tissue was performed using RNA-sequencing. Differentially expressed genes were identified by comparing pretreatment samples of responders with those of non-responders and by pairwise comparison of pre- and posttreatment samples in responders and non-responders, separately. False discovery rate adjusted p-values < 0.05 were considered significant. Significant genes were analyzed by functional data mining.

RESULTS: There was no significant difference when comparing the transcriptional profile of responders with non-responders prior to initiation of bevacizumab therapy. In non-responders, we identified 1 differentially expressed gene using paired analysis of before and after treatment samples. In responders, this approach revealed 236 significantly differentially expressed genes of which 72 genes were down-regulated and 184 genes were up-regulated at time of progression. Genes differentially expressed in responders revealed a shift towards a more proneural and less mesenchymal phenotype at the time of progression. These transcriptional changes were found associated with the in vivo response to bevacizumab treatment.

CONCLUSION: Bevacizumab combination treatment is associated with significant transcriptional changes in responders but not in non-responders. This suggests that non-responders progress due to intrinsic resistance while responders progress due to acquired resistance. Our data suggests that responding glioblastomas undergoes a reverse mesenchymal shift at the time of recurrence, possibly related to down-regulation of TGF-β activity.

P08.07 MICRONRMA REGULATION OF INTRATUMOUR METABOLIC HETEROGENEITY IN GLOBLASTOMA MULTIFORME

H. Allardus, M. Estevez-Cebredo, A. Lourduwamy, R. Grundy, A. McIntyre, S. Smith

University of Nottingham, Nottingham, United Kingdom.

Glioblastoma multiforme (GBM) is the most aggressive and common malignant brain and central nervous system tumour. GBM adaptation to the diverse micro-environmental conditions, including varying degree of vasculature, nutritional supply, oxygen and pH levels, is reflected on its transcriptional and genotypic and metabolic landscape. MicroRNAs (miRNAs) are a class of short non-protein coding sequences that exert post-transcriptional regulation of genes in cells. Understanding the intratumour heterogeneity in miRNA expression will be beneficial to predict the metabolic profiles of glioblastoma.

METHOD: We randomly selected miR-433, belonging to subcluster 14A and 14B. These miRNAs are downregulated in glioblastomas and might have a tumor suppressive role. Any association between the expression levels of cluster 14 miRNAs with overall survival (OS) is undetermined.

RESULTS: Overexpression of miR-323-3p and miR-369-3p, but not miR-433, in glioblastoma cells inhibited their proliferation and migration in vitro studies. Bioinformatics analysis identified 13 putative target genes of cluster 14 miRNAs and real-time RT-PCR validated these findings. Pathway analysis of the overexpressed transcripts identified neutregulin (glial growth factor) as the most enriched pathway. The expression level of cluster 14 miRNAs correlated with the patients’ OS. The median OS was 8 months for patients with low expression levels and 32.5 months for patients with high expression levels (HR = 0.37; 95% CI 0.12–0.64, P = .005).

CONCLUSIONS: The expression level of cluster 14 miRNAs correlates with OS, suggesting a role for cluster 14 miRNAs in preventing aggressive behavior of glioblastoma, possibly through neurregulin signaling.

P08.08 AXITINIB FOR THE TREATMENT OF PATIENTS WITH RECURRENT GLIOBLASTOMA: FINAL RESULTS FROM A RANDOMIZED PHASE 2 CLINICAL TRIAL (AXIG)

D. Duerinck1, S. Du Four1, F. Bontinck2, V. Verschaeve1, C. Andre1, F. Van Freyvenhove1, C. Chaskis3, N. D’haene3, I. Salmon3, B. Neys3

1UZ Brussels, Jette, Belgium, 2AZ Sint-Lucas, Gent, Belgium, 3GHIC, Charleroi, Belgium, 4ULB Erasme, Brussels, Belgium, 52NA Middelheim, Antwerpen, Belgium, 6CHU, Charleroi, Belgium.

BACKGROUND: vascular endothelial growth factor receptor (VEGFR) signal transduction mediates glioblastoma (GB) associated neo-angiogenesis. The AXIG trial (NCT01562197) is a randomized clinical trial that initially investigated the activity of axitinib as a monotherapy (AXI-arm) versus physicians best alternative choice of therapy (Duerinck et al. JNO Mar 2016) and following amendment versus axitinib plus lomustine (Duerinck et al. ASCO AM 2016).

METHODS: an updated pooled analysis was made of the clinical outcome of all patients who initiated treatment with axitinib mono-therapy or axitinib in combination with lomustine in the AXIG trial.

RESULTS: Between August 2011 and July 2015, a total of 78 pts were enrolled in the trial and initiated treatment with axitinib monotherapy (N: 50; AXI) or axitinib plus lomustine (N: 28; AXILOM). Median age was 55y (range 18–80), 50M28F; 19, 29, 19, 7 and 4 pts had a WHO-PS of 0, 1, 2, 3 and 4 respectively. Baseline characteristics were well balanced between study arms (AXI vs AXILOM). All pts had failed prior surgery, RT and TMZ. Thirteen pts in the AXI-arm crossed-over at the time of progression (AXILOM) whereas in the AXILOM-arm 8 pts had an early progression as a decision was generally well tolerated. AXILOM pts were at higher risk for grade 3/4 adverse events (most frequent gr3/4 AE on AXILOM vs AXI were: thrombocytopenia 3- vs 0 pts, hypertension 2 vs 2 pts, anorexia 3 vs 3 pts).

The number of overall tumor responses induced by axitinib was in AXI vs AXILOM. All pts had failed prior surgery, RT and TMZ. Thirteen pts in the AXI-arm crossed-over at the time of progression (AXILOM) whereas in the AXILOM-arm 8 pts had an early progression as a decision was generally well tolerated. AXILOM pts were at higher risk for grade 3/4 adverse events (most frequent gr3/4 AE on AXILOM vs AXI were: thrombocytopenia 3- vs 0 pts, hypertension 2 vs 2 pts, anorexia 3 vs 3 pts).

Peptitides from the invasive edge of GBM tumours produced significantly (P < 0.001) more lactate than established GBM cell lines originally derived from the tumour core. This could reflect the heterogeneity in metabolic adaptation to the tumour micro-environment and cellular phenotype. The resultant highly acidic micro-environment created by the patient-derived GBM cells on their migration potential was assessed using the wound healing scratch assay and the differences in response investigated further using quantitative RT-PCR to identify differences in Epithelial to Mesenchymal Transition (EMT) in glioblastoma patients who were response evaluable and had biomarker assessable tumor tissue surgically removed before axitinib treatment and at time of progression. Patients were grouped into responders (n = 7) and non-responders (n = 14). Gene expression profiling of formalin-fixed paraffin-embedded tumor tissue was performed using RNA-sequencing. Differentially expressed genes were identified by comparing pretreatment samples of responders with those of non-responders and by pairwise comparison of pre- and posttreatment samples in responders and non-responders, separately. False discovery rate adjusted p-values < 0.05 were considered significant. Significant genes were analyzed by functional data mining.

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