of long-term prognosis in a large, single-center series. MATERIAL AND METHODS: Correlations of established clinical (age, sex, tumor location, extent of resection), radiological (postoperative tumor volume) and histopathological parameters (WHO grade, invasion status) were analyzed separately after 3, 5, and 10 years following microsurgery for primary diagnosed intracranial meningioma between 1991 and 2021 and in uni- and multivariate analyses. The prognostic value was calculated in the entire cohort and compared with patients classified as tumor- or necrosis-free after follow-up of 27 months (range: 0-307 months), recurrence was observed in 141 patients (12%) after a median PFS of 36 months. PFS among the entire cohort (n=1218) at 3, 5, and 10 years postoperatively were 96.1%, 90.7%, and 79.4%, respectively. Among all patients with a follow-up of ≥5 years, 4485 patients were classified as tumor- and necrosis-free after a follow-up of ≥5 years, and five years (n=346), respectively. Similarly, postoperative tumor volume was related with recurrence in the entire cohort (p=0.01) but not beyond a follow-up of ≥5 years (p=0.05). In patients with a follow-up of ≥10 years, ten recurrences occurred, and no correlation was found with any of the analyzed variables. CONCLUSION: Skull base tumor location and high-grade histology but not the extent of resection should be considered as parameters influencing long-term survival and interval follow-up ≥25 years after meningioma surgery. Tumor relapses following more than ten years after surgery are very rare, and corresponding predictors are lacking.

P18.02.B. INFLUENCE OF PREOPERATIVE EMBOLIZATION ON INTRAOPERATIVE PARAMETERS, HOSPITAL STAY AND NEUROCognitive OUTCOME COMPARED TO SURGERY ALONE

M. Pedersen1, T. Ebfi2, A. Nania3, H. Voit-Hohne4, M. Schrey2, H. Steiner2, M. Holtmannspöttler2; 1Paracelsus Medical University, Nuernberg, Germany, 2Department of Neurosurgery, Nuernberg, Germany, 3Department of Clinical Neurosciences, Edinburgh, United Kingdom, 4Department of Neuroradiology, Nuernberg, Germany.

BACKGROUND: Preoperative embolization of meningiomas is used to reduce intraoperative blood loss and facilitate resection. So far, a risk-benefit stratification of this additional intervention on the neurocognitive outcome is missing. This study investigates the influence of preoperative embolization with liquid Embolize on intraoperative parameters, length of hospital stays and functional outcome. MATERIAL AND METHODS: Patients treated for primary diagnosed intracranial meningiomas at a single center between January 2019 and June 2021 were reviewed in a retrospective matched-pair analysis. Patients were matched to group A (tumor resected) and group B (preoperatively embolized and tumor resected and ≥5 years follow-up). Matching criteria were tumor diameter (on admission, discharge from hospital and 5 months after embolization), matching criteria tumor diameter (64.21 vs. 63.55 mm, p=0.725) and location (on admission, discharge from hospital and 5 months after embolization), skull base location (HR: 1.51, 95%CI 1.05-2.16; p=0.026), Simpson 2V resections (HR: 2.41, 95%CI 1.52-3.84; p<0.001), high-grade histology (HR: 3.70, 95%CI 2.50-5.47; p<0.001) and male gender (HR: 1.46, 95%CI 1.03-2.11; p=0.045) were independent risk factors for recurrence. Skull base location (HR: 1.92, 95%CI 1.17-3.24; p=0.010) and HR: 2.02, 95%CI 1.04-3.95; p=0.034) but not subtotal resection (HR: 1.53, 95%CI .68-3.45; p=0.303 and HR: 1.75, 95%CI .52-5.96; p=.360) remained independently correlated with recurrence after an event-free PFS of at least three (n=485) and five years (n=346), respectively. Similarly, postoperative tumor volume was related with recurrence in the entire cohort (p=0.01) but not beyond a follow-up of ≥5 years (p=0.05). In patients with a follow-up of ≥10 years, ten recurrences occurred, and no correlation was found with any of the analyzed variables. CONCLUSION: Skull base tumor location and high-grade histology but not the extent of resection should be considered as parameters influencing long-term survival and interval follow-up ≥25 years after meningioma surgery. This study investigated the influence of therapeutic embolization on tumor- and necrosis volume and neurocognitive symptoms in absence of surgical intervention. MATERIAL AND METHODS: Between January 2019 and June 2021, 4 patients (median age 82, 1 female) with 5 radio-graphically suspected intracranial meningiomas, underwent endovascular embolization with liquid embolize and coils, without subsequent surgery. Indication for embolization was history of previous multiple surgery contraindicating further surgical intervention or patients will. Neurological status (on admission, discharge from hospital and 5 months after embolization), medical history, extent of resection, extent of perifocal oedema and symptoms declined to a mild residual paresis. None of the patients showed long-term neurocognitive deficit related to embolization. CONCLUSION: Therapeutic endovascular embolization of radiographic-ally suspected intracranial meningiomas reduced the tumor volume and led to long-term improvement of pre-existing neurocognitive symptoms. In the future, these effects should be verified in larger studies.

P18.04.A. CAY10603, HDAC6 INHIBITOR, ENHANCES RADIOSENSITIVITY IN MENINGIOMA VIA SUPPRESSING THE NUCLEAR BETA-CATENIN ACCUMULATION

Steiner1, T. Holtmannspötter2; 1Paracelsus Medical University, Nuernberg, Germany, 2Department of Neurosurgery, Nuernberg, Germany.

BACKGROUND: Meningioma is the most frequent primary central nervous system tumor (PCNST) which account ca 36% of all PCNST. Due to the lack of efficient chemotherapy for meningioma, radiotherapy often becomes a first-line treatment especially when the tumour is not operable. Radiotherapy plays a crucial role in local control but its efficacy is restricted by radiosistance and by normal tissue radiation tolerance. Therefore, developing and evaluating potential radiosensitisers to enhance therapeutic efficacy are needed. Histone deacetylase (HDACs) expression is generally increased in many cancer types and regulate the expression of numerous proteins involved in tumorigenesis. Targeting HDAC using HDACi inhibitor (HDACi) represent promising radiosensitisers that affect various biological processes, such as cell cycle arrest, DNA repair, cell death using many other mechanisms. MATERIAL AND METHODS: We investigated whether pre-treatment with the hydroxamate-based HDAC6 inhibitor, CAY10603, impacts radiation-induced DNA double-strand break (DSB) induction, cell survival, cell cycle arrest, and cell death using immunocytochemistry, clonogenic assay, and flow cytometry in meningioma cell lines. Low concentration (100 nM) of CAY10603 was treated 24 hr prior to high energy x-ray irradiation (2 Gy) by a medical linear accelerator (LINAC). To investigate the nuclear localisation of β-catenin, subcellular fractionation and Western blot analyses conducted. RESULTS: We found that tumour cells survival was synergistically decreased after combination treatment of CAY10603 and radiation. Combination therapy induced DNA damage with activation of histone h2AX phosphorylation and G2/M arrest compared to drug or radiation alone. Both apoptotic and necrotic cell death were increased after combination therapy. To focus on the mechanisms of action of HDACi inhibition follow by radi-
ation, we further investigated nuclear localisation of beta-catenin levels. The results showed the both beta-catenin and c-myc expression in the nucleus was suppressed after combination therapy. CONCLUSION: In meningioma cells, radiothrapy in combination with HDAC inhibitors reduces the nuclear localisation of beta-catenin and synergistically decreases cell survival. Our findings demonstrate a potential therapeutic strategy of CAY10603 to improve the radiosensitisation for meningioma cells.

P18.05A. BEVACIZUMAB IN ATYPICAL AND ANAPLASTIC MENINGIOMAS: THE BEMEN STUDY

G. Ceretti1, A. Bosso2, M. Maccari2, M. Padovan3, M. Caccen1, V. Zagoni1, G. Lombardi1; 1Veneto Institute of Oncology IOV – IRCCS, Oncology 1, Padua, Italy, 2University of Padova, Medical Oncology School of Specialization, Padua, Italy, 3Veneto Institute of Oncology IOV – IRCCS, Padua, Italy.

BACKGROUND: meningiomas are the most frequent primary brain tumours. The current standard treatment for atypical and anaplastic meningiomas can include surgical resection and radiotherapy. Despite the high rate of relapse no systemic treatment is indicated. Few data are available regarding the effectiveness of bevacizumab (BEV) in this setting. We performed a retrospective analysis investigating the efficacy and safety of BEV in meningioma patients relapsed after receiving surgery and radiotherapy. Gene mutations were also collected. MATERIAL AND METHODS: we retrospectively analyzed patients treated with off-label BEV at the Veneto Institute of Oncology from July 2019 to February 2022. Major inclusion criteria were histologically-confirmed diagnosis of grade 2-3 meningioma (according to WHO 2016 classification), previous treatment as surgery and radiotherapy, and no indication for any additional systemic intervention or retroad, absence of major contraindications to the use of BEV. Data were extrapolated from local clinical records. Bevacizumab was administered at 10 or 5mg/kg every 2 weeks (at physician’s discretion) until progressive disease/death or unacceptable toxicity. Kaplan-Meier curves were used to estimate the survival rate; CTCAE v.5.0 was used to estimate treatment-related toxicities; RANO criteria were used for radiological assessment; NGS Foundation One panel was used to examine molecular data. RESULTS: A median follow up was 15 months (range 1–50). 26 patients were enrolled. Median age was 68 yrs (29–94); male pts were 16 (61%); 16 (61%) pts with atypical meningioma, 38.5% (10 pts) with anaplastic meningioma; 27% (7 pts) had underwent 2 or more surgeries; 58% had had 2 or more RT treatments; 16% (2 pts) received c2 previous lines of systemic treatment. 77% (20 pts) and 23% (6) received BEV 10 and 5mg/kg every 2 weeks, respectively. For 61% of patients (16 pts), NGS analyses were available; 62% (10 pts) harboured NF2 mutations (1 patient had a confirmed diagnosis of neurofibromatosis type 2), 23% (6 pts) CDKN2A/2B deletion, 11% (3 pts) PTEN mutation, 5% (1 pt) CDKIC mutation, 4% (1 pt) NF1 mutation (0.7% 1 pt), 25% (6 pts) characterized by the distinctly lower IC50 value of TK216 exposed cells.

In meningioma (C228T) anaplastic meningioma served as cell model. Additionally, the sensitivity against bevacizumab and TK216 was determined using an MTT-based viability assay (EZAU). To eludicate the effectiveness of TK216 on cell cycle and apoptosis, were stained with PI and annexin V, respectively, and measured by flow cytometry. The effect of TK216 on the protein expression of the cleaved poly(ADP-ribose) polymerases (PARP), indicative for apoptosis, was investigated by western blot. Additionally, a TK216-resistant cell model (BTL695res) was generated and analysed by NGS. RESULTS: BTL695 was significantly more sensitive to TK216 as compared to YK-4-279 (p<0.0001) characterized by the distinctly lower IC50 value of TK216 exposed cells (0.7 mM TK216 and 1.6 mM YK-4-279). Flow cytometry analysis revealed a TK216 induced G2M cell cycle arrest and increased apoptosis rate, which was additionally verified by the expression of cleaved PARP-1 expression using western blot. Genomic aberrations were found in 18 genes including NF2, CDKN2A/B, ARID1A and PTEN. Interestingly, all of the genmic alterations was persistent in the TK216 resistant cell model, a p53 mutation was newly acquired as compared to the parental cell line. CONCLUSION: In summary, our results indicate that ETS transcription factor inhibition by TK216 represents a novel target in meningioma cell model. Additionally, the sensitivity against TK216 is superior to YK-4-279 and therefore TK216 may represent a promising new therapeutic option for patients with aggressive, TERT promoter mutated meningioma.

P18.07. A. HIPPO SIGNALING PATHWAY IS STRONGLY INVOLVED IN MENINGIOMA TUMORIGENESIS

G. Mougel1,2, G. Mondelli3, R. Appay4, A. Querdry5, C. Roche5, A. Jijon1, I. Konstantinova1, A. Soude1, T. Graillon3,2, A. Barlier2,1.

1Marseille Medical Genetics, Aix-Marseille University, Marseille, France, 2Marseille Medical Genetics, Aix-Marseille University, Marseille, France, 3Inventiva Pharma, Daix, France, 4Neurosurgery Department, La Timone Hospital, Marseille, France, 5Inventiva Pharma, Daix, France.

BACKGROUND: Recurrent and aggressive meningiomas remain an unmet medical need in neuro-oncology. In mammals, Hippo signaling pathway is responsible for the growth of organs by regulating cell proliferation and apoptosis. The tumor suppressor NF2 protein belongs to the core of the Hippo pathway and a defect of its gene is present in 50% of meningiomas. Absence of NF2 keeps Hippo pathway inactive allowing the translocation of YAP/TAZ to the nucleus and the formation of a complex with TEA/Dio. This complex then promotes the transcription of anti-apoptotic and proliferative genes such as CTG, CYR61 and AXL. Here, we present an inverse response for the expression of Hippo pathway components and primary cell cultures supporting that Hippo pathway plays a critical role in meningioma tumorigenesis. MATERIAL AND METHODS: The role of the Hippo pathway was studied on 57 meningiomas, well characterized at both histological and molecular level. The genomic profile, target transcripts of the complex YAP/TAZ-TEADs, cell viability, and cell proliferation were analysed after siRNA transfection targeting YAP, TAZ, YAP+TAZ and TEADs. RESULTS: Fifty-seven meningiomas were randomly selected including 27 WHO grade II and III tumors. Thirty (53%) presented a defect on the NF2 gene (NF2def) including 19(65%) grade II/III. NF2def meningiomas presented a significant increase of expression levels of Hippo pathway target transcripts CTG, CYR61 and AXL in comparison with NF2 wild-type tumors (p<0.0001, p=0.0072 and p=0.0191, respectively). This increase was not correlated with the grade, the sex or with the cerebral localization of the meningiomas. On the other side, IHC analysis suggested this increase was correlated with the nuclear localization of YAP. Disturbing the YAP/TAZ-TEADs complex using siRNA on 10 meningiomas (5 NF2 wild-type and 5 NF2 def) induced a significant decrease on cell proliferation but not on cell viability. This decrease was more important when TAZ was turned off in comparison to turning off of YAP. CONCLUSION: Our experimental results strongly support the importance of the Hippo pathway as a new target in meningioma therapy. A.Barlier reports receiving research grants from Inventiva Pharma. No potential conflicts of interest were disclosed by the other authors.

P18.08B. FULLY AUTOMATED MENINGIOMA SEGMENTATION USING 5-WEIGHTED CONTRAST-ENHANCED MR IMAGES ONLY

W. De Raedt1,2,3, W. De Baene1,2,4, J. M. Rutten1, K. Gehring1, E. L. Ongh2, J. M. Touwen5, J. M. Van Rijck3, L. Jijon1,3,4, G. Zagoni1, G. Lombardi1, V. Zagoni1, G. Lombardi1; 1Veneto Institute of Oncology IOV – IRCCS, Padua, Italy, 2University of Padova, Medical Oncology School of Specialization, Padua, Italy, 3Veneto Institute of Oncology IOV – IRCCS, Padua, Italy.

BACKGROUND: Manual segmentation of brain tumors requires expertise, is time-consuming, and is subject to inter-rater variability. Fully automatic brain tumor segmentation is possible for glioma and meningioma when using NGS results might be useful in identifying targetable mutations in case of grade 2-3 meningioma. The treatment was well tolerated. BEV should be considered as potential therapeutic option for patients with aggressive, TERT promoter mutated meningiomas in vitro. METHODS: A meningioma-derived cell line (BTL695) generated from a TERT promoter mutated (C228T) anaplastic meningioma served as cell model for the experiments. TERT promoter mutation was characterized by Sanger sequencing. The in vitro sensitivity of meningioma cells to TK216 was determined using an MTT-based viability assay. RESULTS: BTL695 was significantly more sensitive to TK216 as compared to YK-4-279 (p<0.0001) characterized by the distinctly lower IC50 value of TK216 exposed cells (0.7 mM TK216 and 1.6 mM YK-4-279). Flow cytometry analysis revealed a TK216 induced G2M cell cycle arrest and increased apoptosis rate, which was additionally verified by the expression of cleaved PARP-1 expression using western blot. Genomic aberrations were found in 18 genes including NF2, CDKN2A/B, ARID1A and PTEN. Interestingly, all of the genmic alterations was persistent in the TK216 resistant cell model, a p53 mutation was newly acquired as compared to the parental cell line. CONCLUSION: In summary, our results indicate that ETS transcription factor inhibition by TK216 represents a novel target in meningioma cell model. Additionally, the sensitivity against TK216 is superior to YK-4-279 and therefore TK216 may represent a promising new therapeutic option for patients with aggressive, TERT promoter mutated meningioma.

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