MEDICAL AND NEURO-ONCOLOGY

NO-01. LEPTOMENINGEAL CARCINOMATOSIS AND CONCURRENT BACTERIAL MENINGITIS IN A PATIENT WITH ESOPHAGEAL ADENOCARCINOMA: A CASE REPORT
Lola B. Chambless, Scott L. Parker, Laila Hassam-Malani, Matthew J. McGirt, and Reid C. Thompson; Vanderbilt University, Nashville, TN

INTRODUCTION: Leptomeningeal carcinomatosis (LCCM) is typically associated with systemic malignancies but is not well-studied in the brain. Here we describe a patient who was found to have not only leptomeningeal carcinomatosis from esophageal adenocarcinoma but also concurrent Pediococcus bacterial meningitis. A sixty-six year old man with known esophageal adenocarcinoma, which was previously treated with 5-fluorouracil and cisplatin with concurrent radiation therapy followed by transhiatal esophagectomy, presented sixteen months after initial treatment with failure to thrive and head ache for one month. Diagnostic testing of cerebrospinal fluid revealed adenocarcinoma by cytology and Pediococcus species by culture. Pediococcus causing meningitis is uncommon, previously having been described in only one case report in the English literature. The concurrent finding of both of these conditions in our patient is extremely unusual. It is unknown if the concurrent conditions of leptomeningeal carcinomatosis and Pediococcus meningitis are related or independent conditions. We postulate several possible mechanisms for the causation of this unusual presentation and review recent literature regarding the treatment of these conditions.

NO-02. KARNOFSKY PERFORMANCE STATUS IS A MORE RELIABLE INDICATOR OF PROGNOSIS IN PATIENTS WITH HIGH-GRADE GLIOMA WHEN ASSESSED POST-OPERATIVELY
Lola B. Chambless, Scott L. Parker, Laila Hassam-Malani, Matthew J. McGirt, and Reid C. Thompson; Vanderbilt University, Nashville, TN

INTRODUCTION: High-grade gliomas (HGG) are associated with a poor prognosis even when subjected to aggressive multimodal therapy. Understanding prognostic indicators leads to better risk stratification and more individualized treatment strategies. The Karnofsky Performance Score (KPS) is derived from a scale developed for patients with systemic malignancies but frequently used in this population. Patients presenting with HGG may experience dramatic shifts in performance status between the time of presentation and the early postoperative period. We evaluated the relative reliability of preoperative and postoperative KPS in prediction of prognosis in this population. METHODS: We conducted a retrospective cohort study of 171 patients surgically treated for HGG at a single institution. KPS was recorded from the preoperative and postoperative neuro-oncology assessments or retrospectively calculated if absent. Variables associated with survival in a univariate logistical regression analysis (p < 0.10) were included in a forward selection multiple regression model. Probability values with p < 0.05 were considered significant. RESULTS: Mean age at diagnosis was 55.0 ± 17.3 years. Fifteen (8.8%) patients had a preoperative history of type 2 DM. Fifty-eight (35.8%) patients had a BMI < 25, 55(34.0%) a BMI 25-30, and 49 (30.2%) a BMI > 30. Radiation therapy, temozolomide treatment, and higher postoperative KPS score were independently associated with prolonged survival, whereas old age was associated with decreased survival. After adjusting for these variables, both DM (p = 0.001) and increased BMI (p = 0.003) were independently associated with decreased survival. Diabetics had a decreased median overall survival (312 vs. 470 days, p = 0.003) and PFS (106 vs. 166 days, p = 0.04) compared to nondiabetics. Higher BMI (>25, 25-30, and >30) was also associated with decreased median PFS: 195 vs. 163 vs. 143 days, respectively. CONCLUSION: Preexisting DM and elevated BMI are independent risk factors for poor outcomes in patients with HGG. These conditions should be used in risk stratification in this population and may suggest potential targets of future interventions.

NO-03. TYPE 2 DIABETES AND OBESITY ARE INDEPENDENTLY ASSOCIATED WITH POOR OUTCOMES IN PATIENTS WITH HIGH-GRADE GLIOMA
Lola B. Chambless, Scott L. Parker, Laila Hassam-Malani, Matthew J. McGirt, and Reid C. Thompson; Vanderbilt University, Nashville, TN

INTRODUCTION: High-grade gliomas (HGG) are associated with a poor prognosis even when subjected to aggressive multimodal therapy. Understanding prognostic indicators leads to better risk stratification and may highlight future targets for therapeutic interventions. Type 2 diabetes mellitus (DM) and obesity are known risk factors for poor outcomes in patients with systemic malignancies but are not well-studied in an tumor population. We aim to determine that type 2 DM and elevated body mass index (BMI) are independent risk factors in patients with HGG. METHODS: We conducted a retrospective cohort study of 171 patients surgically treated for HGG (WHO Grade III and IV) at a single institution. Preoperative medical histories were used to calculate BMI and provide records of preexisting DM. Variables associated with survival in a univariate analysis were included in the multivariate Cox model if p < 0.10. Variables with probability values >0.05 were then removed from the multivariate model in a step-wise fashion. RESULTS: Mean age at diagnosis was 55.0 ± 17.3 years. Fifteen (8.8%) patients had a preoperative history of type 2 DM. Fifty-eight (35.8%) patients had a BMI < 25, 55(34.0%) a BMI 25-30, and 49(30.2%) a BMI > 30. Radiation therapy, temozolomide treatment, and higher postoperative KPS score were independently associated with prolonged survival, whereas old age was associated with decreased survival. After adjusting for these variables, both DM (p = 0.001) and increased BMI (p = 0.003) were independently associated with decreased survival. Diabetics had a decreased median overall survival (312 vs. 470 days, p = 0.003) and PFS (106 vs. 166 days, p = 0.04) compared to nondiabetics. Higher BMI (>25, 25-30, and >30) was also associated with decreased median PFS: 195 vs. 163 vs. 143 days, respectively. CONCLUSION: Preexisting DM and elevated BMI are independent risk factors for poor outcomes in patients with HGG. These conditions should be used in risk stratification in this population and may suggest potential targets of future interventions.

NO-04. COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE) V3 TO CTCAE V4: HOW WE SIMPLIFIED THE PROCESS OF CAPTURING ADVERSE EVENTS FOR OUR CLINICAL TRIAL PATIENTS
Kathy Hunter; The University of Texas MD Anderson Cancer Center, Houston, TX

CTCAE V4 has had many changes in terminology and format. As we transitioned from V3 to V4, we realized much of the terminology did not apply to our unique brain/spine patient population and that some of the terms overlapped. We know that when a study is monitored, all terms have to be exact (adverse events [AE] and medication indications must match). The idea was to create an easier, abbreviated version of CTCAE for daily use that would still allow accurate and detailed capture and documentation of adverse events, thus preventing queries during the monitoring process. The first step was to do a side by side comparison of the two versions. An in-service was held to present this comparison to our Clinical Research staff for discussion and input. The next step was to review all of the updated terminology and decide which terms should be used. Lastly, a new pocket sized CTCAE was created and was shared at a subsequent in-service. Because our institution faced staffing issues, it soon became apparent that we needed to simplify some of our daily activities to allow us to work smarter, not harder. Creating this abbreviated version helped all of our team (research nurses and data coordinators) to work more efficiently.

NO-05. OUTCOME OF CONTINUATION OF BEVACIZUMAB FOR RECURRENT GLOBLASTOMA
Marc C. Chamberlain; University of Washington, Fred Hutchinson Research Cancer Center, Seattle, WA

OBJECTIVE: Retrospective evaluation of combination therapy (bevacizumab plus a cytotoxic chemotherapy) following disease progression and treatment with single agent bevacizumab in adults with recurrent glioblastomas and the ability to determine progression free survival (PFS). BACKGROUND: There is no standard therapy for recurrent GBM after failure of bevacizumab. METHODS: 100 adults, ages 36-84 years (median 62), with recurrent GBM were treated. All patients had previously been treated with surgery, concurrent radiotherapy and temozolomide, pre-radiotherapies and were refractory to either...
first (60 patients; 60%) or second recurrence (40 patients; 40%). Patients were treated with bevacizumab, once every 2 weeks and carbotaxil (75 patients; 75%), cyclophosphamide (15 patients; 15%) or BCNU (10 patients; 10%). Neurological evaluation was performed every 6 weeks and neuroradiographic assessment every 2 months. RESULTS: A total of 316 treatment cycles (median 3) of BEV+ were administered, for which there were 74 Grade 3 adverse events (AEs) in 29 patients (29%) and 4 AE grade 4 (1%). Following two cycles of BEV+, 60 (60%) patients demonstrated progressive disease and discontinued therapy. No patient demonstrated a response, although 40 patients (40%) demonstrated neuroradiographic stable response. Survival in the entire cohort ranged from 1 - 12 months with a median of 4 months (95% confidence interval [CI]: 3.9, 4.1). Median and 6-month progression-free survival at 6 months was 2.5 months (range 0.5-6 months; 95% CI: 2.3, 2.7) and 5%, respectively. CONCLUSIONS: Bevacizumab plus a cytotoxic chemotherapy demonstrated limited efficacy and emphasizes an unmet need in neuro-oncology in adults with recurrent bevacizumab-refractory GBM.

NO-06. TOOLS OF THE TRADE: NURSE PRACTITIONER ROLE IN BEVACIZUMAB RELATED TOXICITIES IN GlioBLASTOMA PATIENTS
Eileen M. Le and Eva Lu T. Lee; The University of Texas MD Anderson Cancer Center, Houston, TX

Glioblastoma is a high grade glioma (grade IV), which carries a poor prognosis. The use of bevacizumab (BEV) as targeted therapy (TT) for GBM has shown effectiveness in multiple cancer types, such as colorectal cancer, non-small cell lung cancer, renal cell cancer, and breast cancer. In May 2009, bevacizumab received accelerated FDA approval as monotherapy for patients with recurrent glioblastoma. With the use of TT therapy, there are associated toxicities, which include gastrointestinal perforation, hypertension, cardiac events, proteinuria, and posterior reversible encephalopathy syndrome (PRES) (Higa & Abraham, 2009). Wound healing, hemorrhage, and thromboembolism are known toxicities that are inherent to patients with glioblastoma as well. Thus, it is important to carefully assess subjective and objective complaints given the multitude of toxicities this patient population may encounter due to their primary brain tumor, bevacizumab therapy, or both. As nurse practitioners, we have a unique perspective in caring for glioblastoma patients who are receiving bevacizumab because of our advanced assessment skills, rapport with patients and family members, and clinical experience. Therefore, we must utilize these tools to facilitate our role in patient education, prevention and early detection, monitoring, evaluating, symptom management, and ongoing follow-up regarding bevacizumab-related toxicities.

NO-07. HYDROXYUREA FOR RECURRENT SURGERY AND RADIATION REFRACTORY HIGH-GRADE Meningioma: A RETROSPECTIVE CASE SERIES
Marc C. Chamberlain; University of Washington, Fred Hutchinson Research Cancer Center, Seattle, WA

BACKGROUND: Hydroxyurea (HU), an orally administered chemotherapeutic agent, has become the de facto standard therapeutic agent in patients with surgically and radiation refractory meningiomas based on a limited literature. OBJECTIVES: A retrospective case series of 35 patients with recurrent WHO Grade 2 (n = 22) or 3 (n = 13) meningioma treated with HU following progression after surgery and radiotherapy was conducted with primary study objectives of overall response rate and median and progression free survival (PFS) at 6-months. METHODS: 35 patients (25 women, 10 men; median age 65 years, range 34-86) with recurrent meningioma were treated with HU (1000mg/m2 orally divided twice per day with one cycle operationally defined as 1 month of daily HU). All patients progressed radiographically after prior therapy with surgery (35/35) and radiotherapy (35/35; external beam radiotherapy 35/35; stereotactic radiotherapy 35/35). No patients received prior chemotherapy or targeted therapy before instituting HU. RESULTS: Patients received 0.5-7 cycles (median 2.0) of HU with modest toxicity (28.5% with any grade and 8.5% with grade 3+ anemia or fatigue). There were no radiographic responses; 43% of patients had stable disease and 57% manifested progressive disease at last evaluation. The overall PFS was 3.0% at 6 months (median 2 months; 95% CI: 1.6, 2.4). The majority of patients (80%) following progression on HU were subsequently treated on an investigational trial. CONCLUSIONS: In this retrospective case series, HU was generally well tolerated and convenient but appeared to have very limited activity. This raises questions of what constitutes effective salvage therapy and indicates an unmet need for alternative treatments for recurrent high-grade meningiomas.

NO-08. DIFFUSE LEPTOMENINGEAL RELAPSE FOLLOWING GROSS TOTAL RESECTION IN A SPINAL CORD PILOCYTIC ASTROCYTOMA WITH OLIGOENDROGLIAL FEATURES AND IP19Q DELETION
Zsila S. Sadaghi, Michael L. Pearlman, John M. Slopis, Tribhawan S. Vats, and Soumen Khatua; The University of Texas MD Anderson Cancer Center, Houston, TX

Leptomeningeal dissemination (LMD) occurs in less than 10% of all cases of pilocytic astrocytoma (PA). Most of the metastasis occurs from the brain to the spinal cord. PA with oligodendroglioma (OD)-like features have been reported, but the association of IP19q deletion is extremely rare, so the clinical significance and optimal therapeutic strategy for this tumor subset remains unknown. We report a novel case of a 15-year-old male with NF1 who underwent a whole spine magnetic resonance imaging with a one-month history of neck pain. Neuroimaging showed a localized lesion in the upper cervical spine C3 to C6 with no intracranial involvement. A gross total resection (GTR) was performed, and the pathology was consistent with PA with some OD-like features. Fluorescent in situ hybridization analysis revealed an associated Ip19q deletion. Seven months later, surveillance scans revealed diffuse LMD along the spine with intracranial extension. This case raises some important clinical issues. Firstly, no defined prognostic markers and therapeutic strategy are known in these rare tumors. Observation is recommended in NF1 patients with PA undergoing a GTR. Adjuvant therapy in such tumors is not needed. Whether PA with OD-like features and Ip19q deletion after GTR would benefit from adjuvant radiation or chemotherapy with alkylating agents like temozolomide needs to be profiled. Secondly, prognosis and therapeutic strategy could be enhanced by testing for the BRAF mutation, which is also seen in PA and may control whether these tumors behave more like a PA or an OD. This case typifies the need to embark on identification of correlates of survival, aggressive symptoms and molecular markers for such rare tumors. This would help in deciding the need and type of adjuvant therapy required after GTR to prevent relapses.

NO-09. A RETROSPECTIVE STUDY OF PATIENTS WITH MELANOMA BRAIN METASTASES RECEIVING CONCURRENT WHOLE BRAIN RADIATION AND TEMOZOLOMIDE
Nicholas C. DeVito, Michael Yu, Ren Chen, and Edward Pan;
1University of South Florida, Tampa, FL; 2H. Lee Moffitt Cancer and Research Institute, Tampa, FL

PURPOSE: Metastatic melanoma is the second most common cancer to metastasize to the brain. It is typically treated using stereotactic radiosurgery with or without whole brain radiation therapy. Recently, the alkylating agent temozolomide, which has demonstrated activity in patients with brain metastasis and primary tumors, has been used with concurrent whole brain radiation to delay brain metastasis recurrence, increase survival, and improve the quality of life of patients with brain metastases. Compared to whole brain radiation alone, the addition of temozolomide to whole brain radiation may provide an additional benefit to patients with melanoma brain metastases. METHODS: In this retrospective study, we reviewed the outcomes of 29 patients treated for melanoma brain metastases from 2005 to 2009 at the H. Lee Moffitt Cancer Center. These results were then narrowed via retrospective chart analysis to a cohort of patients with brain metastasis receiving concomitant temozolomide and whole brain radiation. RESULTS: Our study noted a median progression-free survival of 20.4 weeks and an overall survival of 54.4 weeks for patients with melanoma brain metastases, compared to a historical median of 16 weeks with whole brain radiation alone. DISCUSSION: Despite the retrospective nature of this study, it would be useful to further evaluate these interesting findings with a prospective trial utilizing this combined regimen.

NO-10. A PHASE II TRIAL OF EVEROLIMUS IN PATIENTS WITH RECURRENT GlioBLASTOMA Multiforme
Timothy Cloughesy1, J. Raizer2, J. Drappatz3, M. Gerena-Lewis4, J. Rogerio5, S. Yacoub5, and A. Desjardins6; 1Ronald Reagan UCLA Medical Center, Los Angeles, CA; 2Feinsten School of Medicine, Northwestern University, Chicago, IL; 3University of Washington, Fred Hutchinson Cancer Research Center, Seattle, WA

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Glioblastoma multiforme (GBM) is the most common primary adult brain tumor, with approximately 10,000 new cases each year and a mortality rate of over 90% within 2 years. The pathogenesis of GBM is linked to defects in several growth factor signaling pathways, including the phosphatidylinositol 3-kinase (PI3K)-Akt- mammalian target of rapamycin (mTOR) pathway involved in cell survival and proliferation. Everolimus is a mTOR inhibitor that has shown clinical benefit in other malignancies. This 2-arm study aimed to explore the biological effectiveness of 2 doses of everolimus measured by inhibition of N6 phosphoinositide in GBM tumor cells and determine the efficacy and safety of daily everolimus in patients with recurrent GBM. In arm 1, patients received everolimus 0 (n = 6), 5 (n = 6), or 10 (n = 5) mg/day for 7 days or prior to surgical resection, followed with postsurgical everolimus 10 mg/day until disease progression or unacceptable toxicity. In arm 2 patients (n = 24) received everolimus 10 mg/day until unacceptable toxicity or disease progression. Treatment duration was measured in 4-week cycles. The study was terminated early because of low enrollment and disease progression; inhibition of N6 phosphoinositide was not analyzed because of low numbers. There was neither complete remission nor partial response in any patient. The majority of patients in arm 1 and 9 patients (37.5%) in arm 2 had a best response of stable disease, primarily at cycles 2 and 3. Overall for patients in arm 1, the median progression free survival was 14.9 weeks. In arm 2, median progression free survival was 4.1 weeks. Karnofsky performance scores did not change from baseline to study termination. Adverse events were experienced by 88% of patients, serious adverse events by 24%, and 15% of patients withdrew from the study because of drug-related adverse events. In conclusion, efficacy of everolimus in GBM was not demonstrated in this study.

NO-10. A PHASE I STUDY OF TEMOZOLOMIDE AND INTRATHECAL LIPOSOMAL CYTARABINE IN PATIENTS WITH NEOPLASTIC MENINGITIS

Maura D. Gainsch1,2, John DeGroot, Monica Loghin, Charles A. Conrad, Kenneth Hess, Jyssan Ni, Sandra Itech, Kathy Hunter, and WK Alfred Yung; The University of Texas MD Anderson Cancer Center, Houston, TX

INTRODUCTION: We tested the safety of the combination of intraventricular liposomal cytarabine (IVent LC) plus oral temozolomide (TMZ) in patients with neoplastic meningitis (NM). METHODS: Eleven patients were treated. The starting dose of IVent LC was 150 mg/M2 daily, every other week (QOW). Because of severe toxicity in the first 3 patients, the starting dose was changed to 25 mg IVent LC for the first two intrathecal doses, increasing to 37.5 mg and 50 mg in other patients, combined with TMZ at 100 mg/M2 daily increasing to 150 mg/M2 in the last 7 patients. RESULTS: Eleven patients (7 women, 4 men) were accrued. Their cancers were: breast (5), lung (3), melanoma (2), primary CNS lymphoma (PCNSL) (1). Median age was 48 (range 31-59), median Karnofsky performance score was 90 (range 60-100), 10/11 had imaging and 10/11 had cerebral spinal fluid evidence of NM at diagnosis. Grade 3 or 4 toxicities were suffered by 9/11 patients, 6 with hematologic toxicity, 5 with arachnoiditis. Best responses were: not evaluable in 5 (because of death, toxicity, or intercurrent illness), progressive disease in 4, no change in 1, and complete remission in 1 (PCNSL). Median progression free survival was 6 weeks (range 1-32 weeks), median overall survival was 9 weeks (range 1-140+ weeks). One patient with PCNSL cleared the CSF of tumor cells and has remained clear > 140 weeks after additional treatments. CONCLUSIONS: This study demonstrated that the combination of 50 mg IVent LC every 14 days combined with oral TMZ 150 mg/M2 daily QOW was excessively toxic. Lower dosing of each drug was better tolerated but still did not result in favorable outcomes except in one case of PCNSL. Any further investigations of this drug combination and schedule should start at doses no higher than the lowest ones noted above.

NO-12. CNS METASTASES FROM GYNECOLOGIC CANCERS: THE MAYO CLINIC ARIZONA EXPERIENCE FROM 2000-2010

Alex B. Porter1, Amyllus C. Duck, and Nina J. Karlin; Mayo Clinic Phoenix, AZ

Improved treatments for therapy of systemic malignancies have extended patient survival, which has resulted in increased frequency of brain metastases as a cause of gynecologic malignancies. There is a dearth of data in the literature thus far regarding the true prevalence and incidence of these metastases as well as analysis of the optimal treatment for this specific patient population. The main goal was to determine the frequency of CNS metastases as the site of initial recurrence in this patient population. Following institutional review board approval, we performed a retrospective chart review of patients diagnosed with CNS metastases from gynecologic cancers from December 31, 1999 to December 31, 2009. Out of a total of 2,839 gynecologic cancer patients, 14 patients who subsequently developed brain metastases over 10 years. Median time to development of brain metastasis was 38.4 months (95% confidence interval 13.0 - 54.9). Median time between brain metastasis and death was 3.0 months. Whole-brain radiation therapy was used to treat 11 of the 14 patients, of whom 3 had been initially treated with surgical resection followed by radiotherapy (RT). Two of the three patients who had resection followed by RT appear to have extended survival and are alive at the time of the results analysis. This is the largest case series in the literature reviewing brain metastases from gynecologic cancers. The time to death parallels that of brain metastases from other cancers. RT remains a significant part of the treatment for patients with brain metastases. If surgical resection is possible, resection followed by RT appears to be associated with improved survival. The development of novel targeted therapies and small molecule oral agents may hopefully have a role for metastatic ovarian cancer in the future.
Hospita and Dana Farber Cancer Institute, Boston, MA; 19University of Virginia Health System, Charlottesville, VA; 13University of Wisconsin, Madison, WI; 14University of Washington and Seattle Cancer Care Alliance, Seattle, WA; 15Princess Margaret Hospital, Toronto, ON, Canada; 16Albany Medical Center, Albany, NY; 17Kaiser Permanente-Los Angeles Medical Center, Los Angeles, CA; 18Clemenceau Medical Center, Beirut, Lebanon

BACKGROUND: Anaplastic oligodendrogial tumors are rare. Treatment is variable and chemotherapy (CT) and/or radiotherapy (RT) are the most common initial strategies. Median survival varies widely, but it is unclear if this results from prognostic factors or is related to differences in therapy. 1p19q analysis is commonly performed, but it is unclear how to incorporate this and other clinical variables into clinical decision making and prognostication. METHODS: We conducted a retrospective study of 1013 patients treated with various strategies for newly diagnosed disease. Recursive partitioning analysis (RPA) was performed to generate independent prognostic classes among 587 patients with known 1p19q status who were treated initially with CT and/or RT. Variables included for survival classification were: age (continuous), history of prior low-grade glioma, 1p19q deletion status, histology, tumor location, gender, extent of resection, and performance status. Kaplan-Meier curves were plotted to verify classification and tested for significance by log-rank. RESULTS: RPA identified 5 prognostic groups based on hazard similarity: class 1 (age <60, 1p19q codelated), class 2 (<age 43, not codelated), class 3 (age 43-60, not codelated, frontal lobe tumor or age 60-69, not codelated), and class 5 (age >70, not codelated). Survival differences were highly significant (p <0.0001) with medians ranging from 9.3 years (95% CI 8.4-16.6) for class 1 to 0.6 years (95% CI 0.5-0.7) for class 5. CONCLUSION: Five distinct survival groups were defined using RPA modeling of prognostic factors typically obtained during routine management of anaplastic oligodendrogial tumors. Adoption into clinical care and prospective validation may improve therapy for subgroups of patients.

NO-16. 59 YEAR OLD MAN WITH MULTIPLE EXTRACRANIAL METASTASES FROM ANAPLASTIC MENINGIOMA

David Cachia, 1Lloyd Alderson, Richard Moser, Thomas Smith, and Shakeeb Yunus; University of Massachusetts, Worcester, MA

INTRODUCTION: Meningiomas are common, accounting for 20% of all intracranial tumors. The majority are World Health Organization (WHO) grade I, which are typically slow growing, and resection is often curative. Atypical meningiomas (WHO II) are more likely to recur, but this is commonly adjacent to the site of the original disease. Multiple extracranial metastases are very rare. Here we describe a patient who developed multiple extracranial metastases.

CASE REPORT: The patient was a 59-year-old man with a six-month history of headaches. Imaging studies revealed a right frontal extra-axial mass infiltrating the right frontal lobe. Computed tomography of the chest, abdomen, and pelvis were unremarkable. Embolization of the tumor was performed with pathology showing a WHO grade II/III atypical meningioma with a Ki-67 index of 8.9%. A year later, the patient’s surveillance magnetic resonance imaging revealed a large tumor recurrence. The resected tumor showed a WHO grade III/IV anaplastic meningioma with a Ki-67 index of 32%. The patient received radiation (200 cGy × 30). Four months later, the patient suffered a fracture of his left humerus, and x-rays were highly suggestive of a pathological fracture. Biopsy of the site was consistent with atypical epithelioid proliferation. Imaging of the chest, abdomen, and pelvis showed a large mass in the right gluteus maximus muscle and multiple lytic lesions in the ribs, sternum, lumbar vertebrae, and pelvis. Fine needle aspiration and core biopsy of the gluteal mass showed malignant spindle to epithelioid cells. Additional workup included pathology of the chest, abdomen, and pelvis were unremarkable. Fine needle aspiration and core biopsy of the gluteal mass showed malignant spindle to epithelioid cells.

In conclusion, we present a rare case of extracranial metastases of an atypical meningioma that recurred with more invasive features following resection. The pattern of spread in our patient is also rare because the lungs and pleura are quoted in the literature to be the most common site of metastases followed by intra-abdominal organs.

NO-17. EFFICACY AND SAFETY OF TEMOZOLOMIDE ADDED TO RADIOTHERAPY FOR GliOBLASTOMA IN THE ELDERLY

Kamuki Sano1, Akitake Mukasa2, Yoshitaka Narita2, Yusuke Taber1, Nobuhiro Shimoura1, Soichiro Shibui1, and Nobuho Sato1; 1The University of Tokyo Hospital, Tokyo, Japan; 2National Cancer Center, Tokyo, Japan; 3Komagome Metropolitan Hospital, Tokyo, Japan

BACKGROUND: Radiation therapy plus concomitant and adjuvant temozolomide (TMZ) is the standard therapy for the patients with glioblastoma up to 65-70 years of age. However, in elderly patients with glioblastoma, the use of TMZ has been controversial. Although this is partly because of the toxicity of TMZ in elderly patients, the extent of the side effects has not been well evaluated. To clarify the beneficial and adverse effects caused by TMZ in elderly patients, we retrospectively analyzed glioblastoma patients treated with radiation therapy plus TMZ. METHODS: From January 2004 to June 2010, 120 patients with newly diagnosed glioblastoma were treated with this therapy. We divided the patients into an elderly group (age of 65 or older) and non-elderly group (age of younger than 65), and the outcome and toxicity of the therapy were compared between these two groups. RESULTS: A total of 57 patients were classified into the elderly group. The median overall survival and median progression free survival in the elderly group were 15.2 months and 95% confidence interval (CI): 13.1-18.3 and 8.7 months (95% CI: 6.0-11.7), respectively. In log rank analysis, overall survival was significantly shorter in the elderly group than in the non-elderly group (p = 0.029). RPA score and MGMT promoter methylation were prognostic factors for overall survival. Although incidence of overall common toxicity criteria grade 3/4 toxicity in the elderly group was similar to that in the non-elderly group, grade 4 adverse events during concomitant course were more frequent in the elderly group than in non-elderly group (23% versus 8%; p = 0.034). CONCLUSIONS: The addition of TMZ to radiotherapy showed a favorable outcome even in elderly patients with glioblastoma. However, it increased the risk of grade 4 adverse events during the concomitant course, which might shorten the survival of the elderly patients. Optimal use of TMZ to reduce toxicity, especially in concomitant course, should be further clarified.

NO-18. CLINICAL OUTCOME OF GBM LONG-TERM SURVIVORS

Bürgel Flechl, Michael Ackerl, Cornelia Sax, Karin Dieckmann, Richard Grevena, Georg Widhalm, Matthias Preusser, and Christine Marosi; Universal Hospital Vienna, Vienna, Austria

BACKGROUND: An increasing number of patients with glioblastoma multiforme (GBM) are alive longer than three years after diagnosis (long-term survivors). Therefore, there is an urgent need for data about their clinical outcome and quality of life to optimize the medical management and functioning of patients. METHODS: In this cross sectional study, we studied 17 GBM patients surviving for longer than three years. The patients were treated at the outpatient clinic of the Medical University Hospital Vienna. We assessed patients clinical outcome to get global information about the circumstances under which they live 36 months and longer after initial diagnosis of GBM. RESULTS: We assessed 9 female and 8 male GBM long-term survivors with a median age of 51 years (24-71). Fifteen of them lived together with their partner (and children) and 2 lived alone. The mean of the summary-score of the Neuro Cog-Fx, a computerized instrument for neuropsychological assessment of patients with neurological diseases, was 89 (ranging from 66 to 111), for which results from 61-79 are defined conspicuous, 80-89 borderline, and ≥ 90 normal. The global health score ranged from 17% to 100% with a mean of 70%. Drowsiness and fatigue were the most stated physical problems. The Activities of Daily Living Score ranged from 0-8 points with a mean of 7 points, and Barthel Index ranged from 35 to 100 with a mean of 92 points. Six patients showed impairment in their manual dexterity and one patient in mobility. Three patients showed conspicuous depression scores, 2 had conspicuous anxiety results. However, the majority of the GBM long-term survivors is able to manage the activities of daily living independently. Nevertheless, global health and future prospects remain poor.

NO-19. ASSOCIATION OF D-DIMER PLASMA LEVELS WITH MORTALITY RISK IN PATIENTS WITH HIGH-GRADe GliOMA

Christine Marosi, Cihan Ay, Matthias Preusser, Daniela Dunkler, Georg Widhalm, Ingrid Fabinger, Karin Dieckmann, and Christoph Zielinski; Medical University of Vienna, Vienna, Austria

There is evidence for activation of the blood coagulation system in patients with high-grade glioma, which is associated with an increased risk to develop venous thromboembolism (VTE). Interestingly, a systemic activation of blood coagulation and prothrombotic changes in the hemostatic system has been observed even in the absence of VTE and implicated in tumor progression and angiogenesis. Therefore, our aim was to investigate the prognostic value of D-dimer, which indicates global activation of hemostasis and fibrinolysis, for overall survival and mortality risk in patients with high-grade glioma. We have measured D-dimer levels with a D-Dimer latex inhibition assay (D-Dimer Latex, Biococktail, Roche Diagnostics) in 2013 patients with newly diagnosed glioblastoma (grade IV). Median D-dimer level was significantly higher in deceased patients (350 vs. 230 ng/ml, p < 0.001). D-dimer was a significant independent predictor of OS in multivariate analysis with a hazard ratio of 1.76 (95% CI 1.27-2.45). D-dimer levels did not differ in patients with anaplastic astrocytoma (grade III) compared to glioblastoma. D-dimer levels were significantly increased in patients with local recurrence at the time of D-dimer measurement (295 vs. 170 ng/ml, p < 0.001). In conclusion, D-dimer levels might be a valuable independent biomarker for overall survival and mortality in glioblastoma patients and could be helpful in the early detection of patients with a poor prognosis.
agglutination assay in 148 patients with a high-grade glioma (globally glio-
blasta multiforme, median age [25th-75th percentile]: 53 [39-64] years;
53 women and 95 men). These patients were included in the Vienna
Cancer and Thrombosis Study (CATS), an ongoing cohort study
of patients with newly diagnosed cancer or with progressive disease
after remission. They were followed for 2 years until occurrence of VTE
and/or death. Kaplan-Meier and Cox-regression analyses were applied for
statistical calculation. During a median follow-up time of 364 [202-731]
days, 79 (53.4%) patients died and 24 (16.2%) developed VTE. At study
median D-dimer levels were 0.66 [0.34-1.33] µg/ml. The cumulative
survival probability for patients with elevated D-dimer (defined as
more than 0.50 µg/ml) compared to patients with non-elevated
D-dimer (levels < 0.50 µg/ml) were 57% versus 59% after 1 year and
33% versus 43% after 2 years. The univariate hazard ratio of D-dimer
(per double increase) for mortality was 1.2 ([95% confidence interval (CI):
1.1-1.3], p = 0.005) and 1.1 ([95% CI: 1.0-1.2], P = 0.212) in multivariable
analysis after adjustment for age, sex, and VTE. In conclusion, D-dimer
levels were associated with an increased mortality risk in patients
with high-grade glioma. However, this association disappeared after adjustment during multivariable analysis.

NO.20. EXTRANEAL METASTASIS OF A NONGERMINOMATOUS GERM CELL TUMOR OF THE CENTRAL NERVOUS SYSTEM IN A PEDIATRIC PATIENT WITH A VENTRICULOPERITONEAL SHUNT: A CASE REPORT AND REVIEW OF THE LITERATURE
Meghan Belonga and Sachin Jogal; Medical College of Wisconsin,
Milwaukee, WI

Brain tumors are the most common solid tumors in childhood and account
for about 20% of all pediatric malignancies (13, 15). Central nervous system (CNS)
TSGN cell tumors occur in the pineal region (45%) or the suprasellar
region (35%). Germ cell tumors are classified as either germinomas or non-
germinomatous germ cell tumors (NGGCTs). NGGCTs comprise a hetero-
geneous group of histologies including embryonal carcinoma, which is a more
aggressive entity. NGGCTs are less radiosensitive than germinomas, and their
prognosis following standard radiotherapy alone has been poor,
resulting in about a 20-45% overall five-year survival (5, 9). With the
more recent introduction of chemotherapy including both platinum-based
and oxazaphosphorine regimens, the overall four-year progression free survi-
vation (PFS) is currently about 67% (14). Extranearal metastasis (ENM) is a
rarity in central nervous system (CNS) tumors, with an incidence between
0.5% and 2.0% (12, 13, 16, 18). We describe the case of a 7-year-old
Caucasian boy who presented with a mixed malignant germ cell tumor
with predominant embryonal carcinoma component. The patient underwent
right ventriculoperitoneal (VP) shunt placement for hydrocephalus at the
time of diagnosis. He received multigent chemotherapy followed by second-
look surgery. In spite of an initial response to chemotherapy, the patient had
many recurrences of the disease with chemoresistance to platinum. A received
craniospinal radiation and high-dose chemotherapy. Although he had resolu-
tion of CNS disease, follow up off treatment revealed extra-abdominal
metastases. This is a rare case to discuss abdominal metastasis of a CNS
germ cell tumor in a patient with a ventriculoperitoneal shunt. The influence
of VP shunt placement on treatment and management decisions will be
presented.

NO.21. RESPONSE PATTERNS OF HIGH-GRADE GLIOMA PATIENTS TREATED WITH THE TGF-BETA2 INHIBITOR TRABEDERSEN IN A RANDOMIZED PHASE IIIB STUDY
Karl-Hermann Schlingensiepen1, U. Bogdahn2, G. Stockhammer3,
A.K. Mahapatra4, N.K. Venkataramana5, V. Oliushine6, V. Parfenov7,
Masayuki Kanamori, Yoji Yamashita, Mika Watanabe, Chikashi Ishioka,
and Teiti Tominaga; Tohoku University, Sendai, Japan

A recent publication analyzed survival of patients with high-grade gliomas
(HGG) based on WHO grading and isocitrate dehydrogenase 1 (IDH1) gene
status. Applying their strategies, we divided 270 HGGs (115 grade III
gliomas [GIII] and 155 glioblastomas [GBM]) [142 primary GBM, 13 sec-
ondary GBM] experienced at out institution into 4 subsets: GIII with IDH1
mutation (GIII IDH1mut), GIII IDH1 wild-type (wt), GBM IDH1mut, and
GBM IDH1wt. As previously reported, overall survival was the highest in

NO.22. ALTERNATIVE DOSEING MAY IMPROVE CLINICAL OUTCOME IN BEVACIZUMAB-RESISTANT GLIOBLASTOMA
Aaron G. Mammose1, Nicole A. Shonka2, and John F. de Groot3; 1The
University of Texas MD Anderson Cancer Center, Houston, TX; 2University
of Nebraska, Omaha, NE

Bevacizumab (BEV) prolongs progression-free survival in recurrent glio-
blastoma patients; however, at subsequent progression, there is no effective
salvage therapy. There is preclinical evidence to suggest continuous VEGF
inhibition may improve response to chemotherapy. In glioblastoma, some VEGF
activity may limit glioma invasiveness, although the clinical impact of this
approach is unknown. We present preliminary data on alternative BEV
dosing (AD-BEV; 3 mg/kg IV q 3-4 weeks) alone or in combination with
chemotherapy that was initiated in five patients who progressed on standard
dose BEV (SD-BEV; 10 mg/kg IV q 2 weeks). Overall survival (OS) in these
patients from dose adjustment (1st progression on BEV) was compared to 21
patients from MD Anderson enrolled in clinical trials of SD-BEV who transi-
tioned to a non-BEV containing regimen at progression (CG1) and to pub-
lished data in patients continued a SD-BEV containing regimen after
progression (Quant 2009; CG2). Two of 7 patients exhibited DWI changes
coincident with clinical decline and FLAIR/T2 changes at SD-BEV failure,
while subsequent DWI imaging improvement following initiation of
AD-BEV. Median OS from SD-BEV failure in CG1 was 11.7 weeks (95% CI:
7.1-16.3 weeks) and 17.6 weeks in glioblastoma patients in CG2
(Quant 2009, personal communication), whereas median OS for the
AD-BEV cohort was 48.7 weeks (19.1 weeks - 105.6 weeks), with 5 of 7
patients currently alive at the time of writing. Median age was 64, 50, and
motherapy. Median overall survival (mOS) was markedly longer in
trabedersen-treated patients when compared to chemotherapy-treated patients
(details will be presented at the poster). CONCLUSIONS: Trabedersen’s immune-modulatory mode of action results in response pat-
terns distinctly different from those observed with cytotoxic agents. In
trabedersen-treated patients, tumor responses (CR or PR) occur later than
in chemotherapy-treated patients, sometimes after initial stable or transient
progressive disease, but responses are very durable. Tumor control is
achieved rapidly with trabedersen. The mOS after trabedersen treatment is
favorable compared with standard chemotherapy.

NO.23. COMBINATION OF HISTOLOGICAL GRADING AND IDH GENE STATUS CLASSIFIES HIGH GRADE GLIOMAS INTO 4 DISTINCT SUBTYPES: A STUDY OF 270 HIGH GRADE GLIOMAS
Ichiro Shibahara, Tukihiko Sonoda, Toshikazu Kameba, Ryuta Saito,
Masayuki Kamonori, You Yamashita, Mika Watanabe, and Teiti Tominaga;
Tohoku University, Sendai, Japan

Abstracts

Neuro-Oncology • November 2011

iii45

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GILL IDH1mut followed by GBM IDH1mut, GILL IDH1 wt, and GBM IDH1wt (P < 0.05); there was no significance between GBM IDH1mut and GILL IDH1wt. We additionally investigated clinical (age, sex, KPS, Ki67 labeling index [LI], and extent of resection) and molecular factors (MGMT methylation [M] and copy number changes of 1p, 9p, 10q, 19q) in these 4 subsets. As a result, compared to GILL IDH1wt, GILL IDH1mut carried frequent 1p19q codeletions (39%:10%, P = 0.0011) and MGMT M (91%:66%, P < 0.0001) and less frequent 7p gain (11%:33%, P = 0.0045). Compared to GIV IDH1wt, GIV IDH1mut showed frequent MGMT M (82%:44%, P = 0.024). Compared to GIV IDH1mut, GILL IDH1mut showed low Ki67LI (17.0±28.0%, P < 0.0001) and MGMT M (11%:42%, P = 0.041). Compared to GIV IDH1wt, GILL IDH1wt presented low Ki67 LI (23.7±36.7%, P < 0.0001) and less frequent 10q loss (10.4%:0%, P = 0.0003). As a result, for the first time, we present that these 4 subtypes of HGGs carried distinct background. Notably, GILL IDH1wt was a distinct subset both from GILL IDH1mut and GIV IDH1wt, in which a large number of patients.

Neither MGMT M nor IDH1mut was associated with better overall survival (OS) or disease-free survival (DFS) in these 4 subsets, except for the correlation between IDH1mut and OS in GIII IDH1wt messenger RNA (mRNA) expression was significantly lower than GIV IDH1wt in each of the 4 subsets. In HGGs, IDH1mut showed frequent 1p19q codeletions, low Ki67LI, and MGMT M. However, a high number of patients developed increasing right lid ptosis. Magnetic resonance imaging (MRI) showed a new right orbital mass and extensive dural and leptomeningeal enhancement. He was treated with 4 cycles of temozolomide 75 mg/m² per day for 42 days of each cycle, followed by sunitinib 25-37.5 mg for 28 days of each cycle, respectively, which lead to disease stabilization. In 12/10 he developed left leg weakness. MRI showed an increase in size of the right orbital mass and increased nodular and cystic dural enhancement with perilesional edema. He was then treated with bevacizumab 5 mg/kg every 2 weeks. The patient's left leg weakness rapidly resolved and his right paresis improved. MRI after 6 weeks of bevacizumab therapy showed interval reduction in dural contrast enhancement, tumor cyst sizes, and perilesional edema. He continues to receive bevacizumab with stable disease and function after 150 days of therapy. This patient experienced dramatic disease regression following 3 doses of bevacizumab. This is the first report of a tumor response in esthesioneuroblastoma from bevacizumab therapy. This case suggests that antiangiogenic strategies may play a role in salvage therapy for this tumor.
INTRODUCTION: Glioblastoma (GBM) is the most common and aggressive malignant primary brain tumor. For recurrent malignant gliomas, the standard therapy of maximum feasible resection remains dismal. In phase II trials of bevacizumab (Bev) in patients with recurrent GBM, Bev alone or in combination with irinotecan has shown efficacy as measured by objective response rate (ORR) and 6-month progression free survival (PFS). (WHO Grades II-IV) were treated. For the GBM patients, 17 patients were first-relapse and 12 patients were second-relapse. For patients with GBM, the PFS6 was 33.9%, median PFS was 3.3 months, ORR was 27.6%, disease control rate was 79.3%, and median OS was 10.5 months. Six patients who were taking corticosteroids at baseline decreased corticosteroid dosage and two patients discontinued corticosteroids. The most common toxicities (all grade) were proteinuria (41.9%), hypertension (52.8%), and diarrhea (25.8%). Toxicities of grade ≥3 were 41.9%, and the most common of these was hypertension (9.7%). Intracranial hemorrhage was noted in one patient (grade 1). Toxicities led to Bev discontinuation in only two patients (intracranial hemorrhage and neutropenia). No new safety signals for Bev were detected in any patients, and Bev was well-tolerated. CONCLUSION: Bev demonstrated efficacy and acceptable toxicity for Japanese patients with recurrent malignant gliomas.

NO-28. RESPONSE TO BEVACIZUMAB: A ROLE FOR ANTI-ANGIOGENIC THERAPY IN RECURRENT PILOCYTIC ASTROCYTOMA (PA) IN ADULTS
Zulicja S. Sadig, Soumen Khatua, Lauren A. Langford, and Vinay K. Puduvalli; The University of Texas MD Anderson Cancer Center, Houston, TX

Pilocytic astrocytomas (PA) are highly vascular, circumscribed glial tumors that are associated with a good clinical outcome after maximum feasible surgery. Tumor recurrence, although rare, can be associated with a more aggressive biologic behavior that may require the use of chemotherapy or radiotherapy (RT) in addition to surgery. Vascular endothelial growth factor (VEGF) is important for endothelial proliferation and tumor angiogenesis in high-grade gliomas, but its role in PA is less understood. We report the case of a 39-year-old male who presented with a localized left cerebellar enhancing lesion with extension into the brain stem, which yielded a diagnosis of PA after gross total resection. Over the next 4 years, the patient had five local recurrences; the first three were addressed with surgical resection (with no change in histology) with RT administered after the second recurrence. However, the recurrence failed to respond to temozolomide for the patient began a 5/28 day schedule for 1 cycle. Given the aggressive growth of the tumor, bevacizumab was initiated at 10 mg/kg every 2 weeks. MRI scans after a month showed a radiologic response with reduction in the size of both the enhancing and nonenhancing components of the tumor and associated improvement of clinical symptoms. Although higher VEGF expression has been anecdotaly reported in newly diagnosed PA and not recurrent tumor, our patient’s favorable response to bevacizumab suggests that a subset of recurrent PA may be driven by VEGF signaling. Further clinical investigation of anti-angiogenic therapies targeting VEGF for treatment of adult recurrent PA is warranted, including identification of the appropriate agents for this therapy.

NO-29. SALVAGE CHEMOTHERAPY BASED ON O6-METHYLGUANINE-DNA METHYLTRANSFERASE (MGMT) EXPRESSION STATUS FOR RECURRENT MALIGNANT GLIOMAS: EXPERIENCE OF 45 CASES
Dong Shen and Zhong-ping Chen; Cancer Center, Sun Yat-sen University, Guangzhou, China

OBJECTIVE: Expression of O6-methylguanine-DNA methyltransferase (MGMT), which is related to drug resistance in glioma patients. In this study, we analyzed 57 patients with malignant gliomas who received chemotherapy to assess whether chemotherapy based on MGMT expression could be beneficial to patients with MGMT-positive gliomas. METHODS: Fifty-seven patients who were pathologically diagnosed with glioma from August 2000 to January 2006 at Cancer Center of Sun Yat-sen University and received chemotherapy were reviewed. Their cancers included 3 cases of anaplastic oligodendroglioma (AO), 36 cases of anaplastic astrocytoma (AA), and 18 cases of glioblastoma multiforme (GBM). Response and survival time of the patients were evaluated. RESULTS: Thirty-five patients with MGMT positive tumors received chemotherapy regimens that generally consisted of a no-alkylating agent, cisplatin plus TMZ, or a combination of TMZ or nitrosoureas with a no-alkylating agent (teniposide – VM-26, cisplatin, carboplatin[CBP], ifosfamide[IFO], etoposide[VP16]). Twenty-two patients with MGMT-negative tumors received chemotherapy regimens without restriction, i.e., either in combination. There were no significant objective response (OR) and overall response rate (RR) in the patients with MGMT-negative tumors (40.9% and 72.7%) were higher than that in the patients with MGMT-positive tumors (22.9% and 43.6%); there was no statistically significant difference between the two groups (p < 0.05). The progression free survival (PFS) in MGMT-negative and MGMT-positive patients were 8.5 months (95% confidence interval [CI] 4.8-19.3) and 6.7 months (95% CI 3.7-9.3), respectively, and overall survival (OS) was 20.5 months (95% CI 16.1-10 months [95% CI 19-0.05]). CONCLUSION: Our results indicate that personalized chemotherapy for glioma patients based on MGMT expression can give satisfactory results, especially in patients with MGMT-positive gliomas.

NO-30. CHEMOTHERAPY FOR MALIGNANT GLIOMA PATIENTS: A SINGLE INSTITUTION EXPERIENCE WITH 57 CASES
Jun-ping Zhang and Zhong-ping Chen; Cancer Center, Sun Yat-sen University, Guangzhou, China

BACKGROUND: Chemotherapy has been documented to benefit patients with malignant, gliomas. Survival for newly diagnosed O6-methylguanine-DNA methyltransferase (MGMT), which is related to drug resistance in glioma patients. In this study, we analyzed 57 patients with malignant gliomas who received chemotherapy to assess whether chemotherapy based on MGMT expression could be beneficial to patients with MGMT-positive gliomas. METHODS: Fifty-seven patients who were pathologically diagnosed with glioma from August 2000 to January 2006 at Cancer Center of Sun Yat-sen University and received chemotherapy were reviewed. Their cancers included 3 cases of anaplastic oligodendroglioma (AO), 36 cases of anaplastic astrocytoma (AA), and 18 cases of glioblastoma multiforme (GBM). Response and survival time of the patients were evaluated. RESULTS: Thirty-five patients with MGMT positive tumors received chemotherapy regimens that generally consisted of a no-alkylating agent, cisplatin plus TMZ, or a combination of TMZ or nitrosoureas with a no-alkylating agent (teniposide – VM-26, cisplatin, carboplatin[CBP], ifosfamide[IFO], etoposide[VP16]). Twenty-two patients with MGMT-negative tumors received chemotherapy regimens without restriction, i.e., either in combination. There were no significant objective response (OR) and overall response rate (RR) in the patients with MGMT-negative tumors (40.9% and 72.7%) were higher than that in the patients with MGMT-positive tumors (22.9% and 43.6%); there was no statistically significant difference between the two groups (p < 0.05). The progression free survival (PFS) in MGMT-negative and MGMT-positive patients were 8.5 months (95% confidence interval [CI] 4.8-19.3) and 6.7 months (95% CI 3.7-9.3), respectively, and overall survival (OS) was 20.5 months (95% CI 16.1-10 months [95% CI 19-0.05]). CONCLUSION: Our results indicate that personalized chemotherapy for glioma patients based on MGMT expression can give satisfactory results, especially in patients with MGMT-positive gliomas.
even subtly enhancing tumors free of blood products. METHODS: Calculation of dT1 maps is a simple 2-step process. First precontrast and postcontrast anatomic images are standardized using a linear piecewise interpolation method that standardizes the same range over all images such that a particular tissue type falls under the same intensity range. Next, the standardized precontrast image is subtracted from the postcontrast image to output dT1 maps. Also, we qualitatively analyzed more than 80 dT1 maps, corresponding to 48 patients, to determine if dT1 maps would allow tumor detection in 28 consecutive patients. The patients were exposed to SPFM therapy for 1 h daily for 28 consecutive days and were assessed using the Karnofsky performance scale (KPS), Functional Assessment of Cancer Therapy (FACT), and MRI. RESULTS: The statistical analysis revealed a significant correlation between SPFM therapy response and KPS. CONCLUSION: A single exposure of SPFM therapy can detect tumor progression a few months before becoming visible on conventional MRI images. CONCLUSIONS: We report use of a newly developed dT1 method for two main applications: clear delineation of tumor residual upon surgery and early detection of tumor recurrence.

NO-32. RESPONSE OF RECURRENT GlioBLASTOMA TO TARCEVA IN PATIENTS WITH PTEN AND EGFRvIII CONSERVATION

Oscar Gallegos1, Manuel Benavides2, Pedro Perez Segura3, Carme Baladé4, Miguel Gil4, Alfonso Berrocal5, G. Reynes6, J.L. Garcia7, P. Murata1, S. Bague1, and M.J. Quintana1; 1Hospital de Sant Pau, Barcelona, Spain; 2Hospital Carlos Haya, Malaga, Spain; 3Hospital Clínico San Carlos, Madrid, Spain; 4Ico, Barcelona, Spain; 5Hospital General Universitario, Valencia, Spain; 6University de Cervera, Spain; 7Hospital de Valencia, Spain; Hospital Ramon Y Cajal, Madrid, Spain

BACKGROUND: The epidermal growth factor receptor (EGFR) is commonly amplified, overexpressed, and mutated in glioblastoma (GBM). Efficacy of anti-EGFR treatments have shown to be associated with EGFR deletion mutant variant III (EGFRvIII) and expression of PTEN (Phosphatase and Tensin homolog deleted on chromosome 10). We conducted a phase II study to evaluate the efficacy of tarceva treatment in patients with relapsed GBM. METHODS: To date 14 patients have been treated. All the patients were PTEN (+++) and EGFR (++++), and EGFRvIII (+++) by immunohistochemistry. One patient had a brain tumor with a EGFRvIII without PTEN. Eligibility criteria were histologically proven GBM, radiologic progression, >18 years old, Karnofsky performance score ≥70, and adequate bone marrow and organ function. There was no limit on the number of prior relapses. No enzyme-inducing antiepileptic drugs were allowed. The primary endpoints were response rate and progression-free survival at 6 months.RESULTS: We have treated 14 patients with recurrent GBM (7 man/7 women) with 150 mg of tarceva daily. Median age was 55 years. Median KPS was 80 and median number of prior relapses was 2. One partial response and 3 instances of stable disease have been reported to date. One patient remains stable at 18 months. PF58 was 10%. Median PF58 was 1.6 months (0.96-2.3). Dose reduction was not necessary. The main treatment-related toxicity was diarrhea, reported in 11 patients (71%) and 2 in 3 patients. Any grade 3 toxicity was documented. Median survival was 5 months (confidence interval [CI]0.2-9.8). Correlation IHC, FISH, and PCR will be reported. CONCLUSIONS: Treatment with 150 mg daily of tarceva in GBM relapsed with PTEN (++) and EGFRvIII (+++) by immunohistochemistry showed minimal efficacy with low toxicity.

NO-33. EFFECT OF SEQUENTIALLY PROGRAMMED MAGNETIC FIELD (SPFM) THERAPY IN THE TREATMENT OF PRIMARY MALIGNANT BRAIN TUMOURS

V.G. Vasshita; SBF healthcare & Research Centre Pvt. Ltd., Bangalore, India

INTRODUCTION: A study to demonstrate the efficacy of SPFM therapy on 123 terminally ill cancer patients was published in Journal of the Science of Healing Outcomes in 2008 and showed promising results that substantiated the effectiveness of this therapy. This article demonstrates the efficacy of this new therapeutic modality, in treatment of brain tumors without any side effects. METHODS: 50 terminally ill patients from the subgroup with primary malignant brain tumors were included for the study. 5 out of 50 were from the pediatric age group. All the patients had completed standard modalities of treatment such as surgery or radiation with or without chemotherapy and palliative care. The patients were not non-surgical candidates. RESULTS: The patients were exposed to SPFM therapy for 1 h daily for 28 consecutive weeks. Eligibility criteria were histologically proven GBM, KPS ≥70, and radiologic progression. We report weaning a 13 year old boy with radiation necrosis off steroids with good symptom control using bevacizumab. The boy was diagnosed to have radiation necrosis using a T1-weighted MRI of the brain with gadolinium enhancement and FLAIR technique a few weeks after he received radiation therapy with 5400 cGy in 27 fractions and a boost of 900 cGy over a year later. Vascular Endothelial Growth Factor (VEGF) is known to increase capillary permeability and worsen edema in radiation necrosis. Bevacizumab is a monoclonal antibody against VEGF. Although there have been a few case series regarding the effectiveness of bevacizumab in the treatment of radiation necrosis in adults, we could find only one other such study for the pediatric population. Bevacizumab can be an effective therapy in the treatment of
radiation necrosis in children without the side-effects encountered with steroid therapy. Further study is warranted on the dosage, frequency, duration, and safety of treatment with bevacizumab for cerebral radiation necrosis in children.

NO-36. PHASE I / II ADAPTIVE RANDOMIZED TRIAL OF VORINOSTAT, ISOTRETINOIN, AND CARBOPLATIN IN ADULTS WITH RECURRENT GliOBLASTOMA MULTIFORME - RESULTS OF THE PHASE I ARM
Vinay K. Puduvalli, Marta Penas Prado, Kenneth R. Hess, Kathy Hunter, Sandra Ictech, Morris D. Groves, Mark R. Gilbert, Vivien Liu, Charles A. Conrad, John de Groot, Monica E. Lohgian, Howard Colman, Victor A. Levin, and W.K. Alfred Yung; The University of Texas MD Anderson Cancer Center, Houston, TX

BACKGROUND: Therapeutic strategies against malignant gliomas have focused on DNA-damaging agents, antiangiogenic strategies, and signal transduction pathways. However, epigenetic processes such as DNA methylation and histone acetylation constitute novel therapeutic targets against gliomas. Vorinostat, a histone deacetylase inhibitor (HDACi), has shown preliminary activity in adults with recurrent glioblastoma. Based on the preliminary and tolerability results of the phase I study, we hypothesized that combining these agents with vorinostat would improve outcome in malignant gliomas. We report the final results of the phase I study of combinations of these agents preceding a 3-arm adaptive randomized phase II study. METHODS: Adults with recurrent malignant glioma, KPS ≥ 60, normal organ function, and no prior exposure to HDACi or carboplatin were enrolled into three treatment arms: vorinostat + isotretinoin (Arm-1), carboplatin + isotretinoin (Arm-2), or vorinostat + isotretinoin + carboplatin (Arm-3). Dose escalation was done in 3 + 3 design declaring MTD at the highest dose causing DLT in <2/6 patients. RESULTS: Toxicities among 43 evaluable patients included: Arm1-neuropenia, thrombocytopenia, pulmonary embolism, elevated AST (DLT) and hypertriglyceridemia (DLT); Arm2-neutropenia, thrombocytopenia (DLT) and hypokalemia (DLT); MTD were established for Arm-1 (vorinostat 400 mg/d, days 1-7 and 15-21, isotretinoin 100 mg/m2 x21d) and Arm-2 (carboplatin AUC4, isotretinoin 100 mg/m2 x21d). Arm-3 required dose de-escalation to level -3 (vorinostat 300 mg/d, days 1-7 and 15-21, isotretinoin 100mg/m2 x21d, carboplatin AUC4) because of DLT (grade 3/4 thrombocytopenia) at dose level 2. Six patients achieved progression free survival at 6 months (1 in Arm-1, 2 in Arm-2 and 3 in Arm-3). CONCLUSIONS: Although the 2-drug combination MTDs were established, the 3-drug combination of vorinostat + isotretinoin + carboplatin had significant toxicities precluding further testing despite preliminary evidence of activity in these heavily pretreated patients. The trial has been modified, replacing carboplatin with dose-dense temozolomide, and restarted with a lead-in phase I to be followed by a multicenter Bayesian adaptive randomized phase II study.

NO-37. CENTRAL NERVOUS SYSTEM ANGIOSARCOMA: DIAGNOSIS AND TREATMENT
James R. Hackney, Cheryl A. Palmer, James M. Markert, Joel Cure, Kristen O. Riley, Hassan Fathallah-Shaykh, and L.B. Nabors; University of Alabama at Birmingham, Birmingham, AL

Primary CNS angiosarcoma is an extremely rare malignancy with approximately 17 cases reported in the literature in the last 25 years. This tumor is characterized by a high rate of local recurrence and a short median survival time. Therapy has been limited to surgical resection with or without radiation therapy, because of the conventional wisdom that sarcomas are generally not sensitive to chemotherapy. We report two cases of primary CNS angiosarcoma in an attempt to develop a rational approach to diagnosis and treatment given the rarity of this entity. A 35-year-old woman presented with exophthalmos that progressed over six months. Imaging studies demonstrated a homogenous mass of the left retro-orbital area with peripheral enhancement. An initial attempt at surgical resection was aborted because of severe bleeding, but a second procedure following tumor embolization was successful. The second patient was a 47-year-old man who presented with sudden visual loss in the left eye. Imaging studies revealed a heterogeneously enhancing left sphenoid wing mass extending into the sphenoid sinus and nasal cavity. An initial attempt at surgical resection resulted in a near-gross total resection. In both cases, neuropathological examination demonstrated angiosarcoma. No other primary sites were identified, and these two cases were not related to any other malignancies. The first patient is doing well without progression at ten-month follow-up after completing radiation therapy with concurrent bevacizumab. The second patient exhibits no residual disease one month post-surgery. The therapy plan calls for radiation therapy, temozolomide, and bevacizumab. The paucity of relevant studies of primary CNS angiosarcoma precludes definitive judgment concerning optimal therapy; however, the literature suggests that surgery with an emphasis on gross total resection remains the standard of care. There may be a rationale for the use of antiangiogenesis agents such as bevacizumab or other newer chemotherapy agents. Finally, postoperative radiation therapy may provide benefit, particularly when gross total resection is not possible.

NO-38. A RETROSPECTIVE ANALYSIS OF THE EFFICACY AND TOLERABILITY OF LACOSAMIDE IN PATIENTS WITH BRAIN TUMOR
Marlon G. Sarna1, Courtney Corle1, Jethro Hu2, Jeremy Rudnick2, Suranjan Prabhakaran1, Maciej M. Mrugala1, Laura K. Lee1, Beverly D. Fr0, Daniela A. Bota4, Ryan Y. Kim1, Tiffany Brown1, Homira Feely1, Alexander Hu1, Jan Drapparte1, Patrick Y. Wen1, Jong W. Lee1, Bob Carter1, and Santoshi Kesari1; 1UC San Diego, La Jolla, CA; 2Cedars Sinai Medical Center, Los Angeles, CA; 3University of Washington, Seattle, WA; 4University of Irvine, Irvine, CA; 5Brigham and Women’s Hospital, Boston, MA

BACKGROUND: As many as 30% to 50% of brain tumor patients present with seizures, and many more remain at risk of developing seizures over the disease course. The management of seizures in these patients is complicated by tumor growth and the numerous adverse effects and drug interactions of traditional anti-epileptic drugs (AEDs), which are seen more frequently in patients with brain tumors than with other brain lesions. To the best of our knowledge, there have been no published studies looking at the efficacy and tolerability of lacosamide in controlling seizures in patients with brain tumors. AIM: To determine the efficacy and tolerability of lacosamide in brain tumor patients with brain tumors. DESIGN: We performed a retrospective chart review of the medical records of all patients with a diagnosis of a primary brain tumor who were placed on lacosamide at 5 academic medical centers with tertiary brain tumor programs in the U.S. The main outcome measures were seizure frequency and toxicities. RESULTS: A total of 51 patients were identified and included in this study, the majority of the patients had gliomas (95%). Fifty-five (97%) patients had partial seizures only, and 12 (17%) had generalized seizures. Most (74%) of the patients were started on lacosamide because of recurrent seizures. Forty-one (80%) patients reported stable seizures, and 21 (30%) reported stable seizures. Most of the patients (n = 54, 77%) placed on lacosamide did not report any toxicities. DISCUSSION: The newer AEDs, lacosamide has not been evaluated in a population of patients with brain tumors. Our retrospective analysis demonstrated that lacosamide was both effective and well tolerated as an add-on AED in patients with brain tumors. Lacosamide’s novel mechanism of action will allow for concurrent use with other AEDs as documented by its efficacy across many different types of AEDs used in our population.

NO-39. INTRAOCULAR LYMPHOMA DEVELOPED AFTER SALVAGE CHEMOTHERAPY FOR RECURRENT PRIMARY CNS LYMPHOMA AND PROMISING THERAPY - A CASE REPORT
Beverly Dan Fu, Xiao-Tang Kong, and Daniela A. Bota; UC Irvine Medical Center, Orange, CA

Intraocular Lymphoma (IOL) is a subset of primary central nervous system lymphoma (PCNSL), a rare form of non-Hodgkin’s B-cell lymphoma. The frequency of IOL has been rising in immunocompetent patients. We report the challenges of obtaining a diagnosis and the treatment of a female patient who has developed IOL after three cycles of salvage therapy with intravenous methotrexate for her recurrent PCNSL. A 68-year-old woman was diagnosed with a large B-Cell central nervous system lymphoma in 2005 by brain tumor biopsy. She was in remission after 5 cycles of high-dose methotrexate for three years. The patient received two additional courses of methotrexate for recurrences 3 and 4 years after the initial diagnosis. Four and a half years after the PCNSL diagnosis, she developed vitritis and received high dose solumedrol with very slight improvement. CSF cytology was negative. A vitrectomy of her right eye was performed, and pathology showed CD-20 positive large B-cells with very slight improvement. CSF cytology was negative. A vitrectomy of her right eye was performed, and pathology showed CD-20 positive large B-cells. Immediately following the diagnosis of IOL, we started her on intravenous rituximab and oral temozolomide concomitant with intravitreal injection of rituximab. Eventually, the temozolomide was discontinued because of hematologic toxicities. The patient had a total of 4 intravenous rituximab and 8 intravitreal rituximab treatments in both eyes. Her retreat ed vitreous biopsy showed no malignant cells. Her visual acuity has no further deterioration. IOL should be suspected in patients who present with vision impairment and have a history of PCNSL. CSF study might be negative in most of the patients with isolated IOL or even with PCNSL. Vitreous surgery or vitrectomy with corresponding pathology still the gold standard.
in the diagnosis of primary intracranial lymphoma. Intravital rituximab injection concomitant with systemic rituximab and temozolomide might be a promising therapy for IOL. Further study of more cases is warranted.

**NO-40. OPTIC NEUROPATHY IN GLIOMA PATIENTS AFTER RECEIVING RADIOTHERAPY AND BEVACIZUMAB: RISK FACTORS AND RELATED QUALITY OF LIFE ISSUES**

Beverly Dan Fu and Daniella A. Bota; UC Irvine Medical Center, Orange, CA

Focal beam radiation in combination with temozolomide is the standard treatment for malignant gliomas as well as nonresectable, high-risk WHO grade II gliomas. Bevacizumab treatment at time of recurrence is stipulated to increase the patient’s survival. However, optic nerve neuropathy is one of the serious complications of radiotherapy, and there are very few articles that discuss the relationships between bevacizumab and optic nerve neuropathy in the patients who develop bilateral optic nerve neuropathy during or after their treatment. The purpose of this study is to identify cases of bilateral optic nerve neuropathy in patients that received focal radiation and bevacizumab and to delineate possible risk factors and related quality of life issues. The data collection protocol is approved by Institutional Research Board at University of California, Irvine. Two patients with bilateral optic neuropathy after receiving focal beam radiation and bevacizumab were identified. Both patients were started on bevacizumab due to their tumor progression 2 months after completing radiation therapy, and the median time from the end of radiation to the onset of visual decline was 10.5 months. Case #1 is a 70-year-old Hispanic man with a nonresectable, bifrontal LGO who developed bilateral optic nerve neuropathy 7 months after starting on bevacizumab. Case #2 is an 82-year-old Asian man with the diagnosis of left frontal GBM who developed bilateral optic nerve neuropathy 13 months after the initiation of bevacizumab. Their mean radiation dose to the optic chiasm was 49.64 Gy. Focal beam radiation, as well as bevacizumab, plays an important role in the treatment of gliomas. However, it is important for patients with the diagnosis of glioma who are started on bevacizumab shortly after radiation to have routine follow-up with neuro-ophthalmologist consultation, home health safety evaluation, clinical social worker involvement, and periodical MRI of the orbits if their symptoms warrant.

**NO-41. EVEROLIMUS TREATMENT OF SUBEPENDYMAL GIANT CELL ASTROCYTOMAS (SEGAs) ASSOCIATED WITH TUBEROUS SCLEROSIS COMPLEX (TSC): THE EXIST-1 TRIAL**

Steven Spargaro1, E. Belousova2, Sergiusz Jozwik1, Bruce Korf1, Michael Frost1, Rachel Kuperman1, Michael Kohrman1, Olaf Witt1, Joyce Wu2, Robert Flammia1,19, Anna Jansen2,20, E. Thiele1, VA Medical Center Tucson, Tucson, AZ;11Queens University, Kingston, ON, Canada;12Children's National Medical Center, Washington, DC;13Massachusetts General Hospital, Boston, MA;14Tubero-Sclerosis Alliance, Silver Spring, MD;15Neurodevelopmental Research Group, University of Alabama at Birmingham, Birmingham, AL;16Epilepsy Group, St. Paul, MN;17Children's Hospital and Research Center Vega, Rome, Italy;18University of North Carolina at Chapel Hill, Chapel Hill, NC;19The Children's Hospital of Boston, Boston, MA;20Penn State Children's Hospital, Hershey, PA;21Global Alliance for Tuberous Sclerosis, Rome, Italy;11Massachusetts General Hospital, Boston, MA;22Clinical Research Unit, Melbourne Hospital, Parkville VIC, Australia

**TUBEROUS SCLEROSIS COMPLEX (TSC): THE EXIST-1 TRIAL**

**GIANT CELL ASTROCYTOMAS (SEGAs) ASSOCIATED WITH their symptoms warrants.**

**BACKGROUND:** Prognosis of recurrent MG is poor. Historic data from phase II trials in patients failing RT +/- TMZ with traditional D1-5 TMZ reported 6 months progression free survival (6mPFS) between 15-20% and median overall survival (OS) of 6-7 months. Based on the favorable toxicity profile, alternative TMZ (metronomic, dose intense, and dose-dense) schedules are possible and may overcome MGMT mediated resistance and down-regulate angiogenesis. METHODS: The criteria used to identify relevant studies through literature search were clinical trials of MG using TMZ schedules other than D1-5 Q 28d. RESULTS: Ten studies were retrieved. POOLED ESTIMATES: Based on published data of survival estimates, were obtained according to standard meta-analysis procedures. Sensitivity analyses were performed to examine whether outcomes were associated with previous treatment. RESULTS: 6mPFS for all studies was 30% (95% CI 26-34) and 27% (95% CI 22-31) for the 8 studies not including chemotherapy-naive patients. OS data was available from 8 studies yielding a 12 month OS of 37% (95% CI 32-42) and 41% (95% CI 38-47) in 6 studies that excluded chemotherapy-naive patients. All studies reported that alternative TMZ schedules were well tolerated. CONCLUSIONS: Heterogeneity and lack of a control arm make the interpretation of these studies difficult. However, the magnitude of 6mPFS and OS outcomes were similar across trials, and there is a modest benefit associated with alternative schedules of TMZ.
NO-44. ENDOCRINOLOGICAL EVALUATION OF THE EFFICACY OF GAMMA KNIFE RADIOSURGERY FOR RECURRENT TUMOR IN CAVERNOUS SINUS AFTER TRANSSPHENOIDAL RESECTION OF GROWTH HORMONE SECRETING PITUITARY MACROADENOMA

Minschul Oh, Eunhyun kim, and JongHee Chang; SunHo Kim, sevance hospital, seoul, Korea, Republic of

The object of this study is to determine long-term effect of gamma knife radiosurgery (GKS) for the treatment of remnant tumor in the cavernous sinus (CS) after transphenoidal surgery (TSS) of growth hormone (GH)-secreting pituitary macroadenoma. Seventeen patients who failed to achieve biochemical remission after TSS were followed for a mean period of 70.2 months (range 17-180) after GKS. All patients underwent regular hormonal examination including serum GH, IGF-1, oral glucose tolerance test, and combined pituitary function test (CPT). Magnetic resonance imaging was performed 1-year after GKS and then at subsequent 1.5-year intervals. All remnant tumors were confined in the CS and treated with hormone-suppressive medication, sandostatin LAR before or after GKS. There were 13 women and 4 men with a mean age of 41.8 years (range 27-62). Ten patients (58.8%) achieved hormonal remission with a mean time of 47 months (median 40, range 18-129) after GKS, and mean marginal radiation dose was 27.9 Gy (range 14-33). Mean tumor volume decreased from 5.15 ml (pre-GKS) to 3.55 ml (last follow-up) (p = 0.000). Actual rates of remission at 2, 4, and 6 years were 12.5%, 40%, and 64%, respectively. Intergroup comparison between the remission and non-remission groups revealed that those who had a minimum hormonal follow-up period of 48 months showed significant difference in both serum level of GH (p = 0.023) and degree of decreased GH percentile (p = 0.014) at 12 months after GKS. A significant new pituitary hormone deficiency after GKS was found only in the gonadal axis (p = 0.032) based on last follow-up CPT. Radiation necrosis was detected in 4 patients. GKS in remnant tumor restricted to the CS after maximal resection of tumor in the sellar and supraellar area is effective, especially for minimizing newly developed post-GKS hypopituitarism. However, care should be taken to avoid radiation-induced adjacent lobe necrosis after GKS in the CS.

NO-45. IDH MUTATIONS AND THEIR ROLE IN PROGRESSION OF LOW GRADE GLIOMAS

Tareq A. Juratli, Matthias Kirsch, Gabriele Schackert, and Dietmar Krex; University Hospital Dresden, Dresden, Germany

Somatic mutations in the gene encoding isocitrate dehydrogenase 1/2 (IDH1/2) are frequently found in secondary malignant gliomas and are of prognostic value. It is still unclear whether IDH mutation status changes during the progression from low-grade (LGG) to secondary high-grade gliomas (sHGG). Samples of patients with LGG (WHO grade II) and their later sHGG were investigated. IDH1/2 mutation and MGMT promoter status were analyzed. The data were categorized according to demographic parameters, tumor-related factors, therapy-related factors, and patients’ survival. Our population comprised 100 patients. Median follow-up was 9.6 years. We investigated 45 sample pairs of LGG and their later sHGG. IDH1/2 mutations were found in 36/45 LGG (80%) and matching sHGG without any changes in the mutation status. Patients with IDH mutations showed a significantly improved OS (9.3 vs. 3.8 years) but no superior PFS or time to malignant transformation. Secondly, samples of 72 patients with sHGG (30 AA and 42 GBM) were analyzed. 53/72 (73.6%) patients harbored IDH1/2 mutations. The presence of IDH mutations after malignant transformation correlated with significantly improved PFS (2.2 vs. 1.0 years, p = 0.003) and OS (8.7 vs. 4.3 years, p = 0.005). Patients with IDH mutations and methylated MGMT promoter had the longest OS. Thirdly, 75 patients with LGG were analyzed. 45/73 patients (61.6%) developed sHGG. Except for extent of surgery and patients’ age (p = 0.001), all investigated factors (tumor location, IDH mutaton and MGMT promoter status, radiation and chemotherapy regimen, age, and extent of surgery criteria. Toxicity (somatic mutations) show a strong association with superior OS or PFS in the multivariate analysis. The IDH mutation status is stable during the progression of LGG to sHGG. IDH mutations are a good prognostic marker for sHGG according to PFS and OS, but are not of clinical prognostic relevance in the low-grade stage. Patients with LGG only benefit from IDH mutations after malignant transformation.

NO-46. RT0G 0525: A RANDOMIZED PHASE III TRIAL COMPARING STANDARD ADJUVANT TEMOZOLOMIDE (TMZ) WITH A DOSE-DENSE (DD) SCHEDULE IN NEWLY DIAGNOSED Glioblastoma (GBM)

Mark R. Gilbert1, Meihsia Wang2, Ken D. Aldape3, Roger Stupp4, Monika Hegi5, Kurt A. Jackel6, Terri S. Armstrong7, Jeffrey S. Wefel8, Miehun Won9, Deborah T. Blumenthal9, Anita Mahajan10, Christopher J. Schuler10, Sara C. Erdrige11, Paul D. Brown12, Arnab Chakravart12, Walter J. Curran, Jr.13, and M尼斯he P. Mehta14; 1M. D. Anderson Cancer Center, Houston, TX; 2RT0G Statistical Center, Philadelphia, PA; 3University of Lausanne Hospitals (CHUV), Lausanne, Switzerland; 4Mayo Clinic Florida, Jacksonville, FL; 5University of Texas Health Science Center Schiller, Nursing, Houston, TX; 6Tel-Aviv Sourasky Medical Center, Tel Aviv, Israel; 7Medical College of Wisconsin, Milwaukee, WI; 8University of Edinburgh, Edinburgh, United Kingdom; 9Arthur G. James Cancer Center, The Ohio State University, Columbus, OH; 10Emory University, Atlanta, GA; 11Northwestern University, Chicago, IL

Radiotherapy with concomitant and adjuvant TMZ is the standard of care for newly diagnosed GBM. MGMT methylation status may be an important determinant of treatment response. This trial, conducted by the RT0G, EORTC, and NCCTG, determined if intensified TMZ improves survival (OS) or progression free survival (PFS) in all patients or specific to MGMT status. Eligibility criteria included age > 18 yrs, KPS > 60, and existence of a tumor for preoperative MRI. 1231 patients were randomized to Arm 1: standard TMZ (150-200 mg/m2 x 5 d) or Arm 2: dd TMZ (75-100 mg/m2 x 21 d) for 6-12 cycles. Symptom burden, quality of life (QOL), and neurocognition were prospectively and longitudinally assessed in a patient subset. 832 patients were randomized (1173 registered). Inadequate tissue (n = 144) was the most frequent reason for nonrandomization. No statistical difference was observed between Arms 1 and 2 for median OS (16.6, 14.9 mo, p = 0.63), median PFS (5.5, 6.7 mo, p = 0.06), or methylation status. MGMT methylation was associated with improved OS (21.2, 14 mo, p < 0.0001), PFS (8.7, 5.7 mo, p < 0.0001), and treatment response (p = 0.012). Cox modeling identified MGMT status and RPA class as significant predictors of OS; treatment arm and radiation technique (EORTC vs. RT0G) were not. There was increased grade ≥ 3 toxicity in Arm 2 (19%, 27%, p = 0.008), which was mostly lymphopenia and fatigue. This study did not demonstrate improved efficacy for dd TMZ for newly diagnosed GBM patients. However, dose-dense TMZ showed a significant improvement of MGMT methylation in GBM, demonstrated the feasibility of tumor tissue collection, molecular stratification, and collection of patient outcomes in a large transatlantic intergroup trial, thereby establishing a viable clinical trial paradigm. Support: NCI U10 CA 21661 and U10 CA37422.

NO-47. RANDOMIZED PHASE II STUDY OF NEOADJUVANT BEVACIZUMAB AND IRINOTECAN VERSUS BEVACIZUMAB AND Temozolomide FOLLOWED BY CONCOMITANT CHEMORADIOTherapy IN NEWLY DIAGNOSED PRIMARY Glioblastoma Multiforme

Kenneth F. Holland1, Steinbjörsnótt Hrund2, Morten Sørensen3, Henrik Schøtz4, Rida Mahhi5, Silke Engelholm6, Anders Ask3, Charlotte Kristiansen7, Carsten Thomsen8, Hans S. Poulsen8, and Ulrik N. Lassen1; 1Rigshospitalet, Copenhagen, Denmark; 2Odense University Hospital, Odense, Denmark; 3Aarhus Hospital, Aarhus, Denmark; 4Roskilde Hospital, Roskilde, Denmark; 5University Hospital of Lund, Lund, Sweden

First-line temozolomide (T) and radiotherapy is standard in glioblastoma multiforme (GBM). In second-line therapy, the combination of bevacizumab (B) and irinotecan (I) produces impressive responses. We investigated the efficacy of BT and BI. Newly diagnosed GBM patients were randomized to neoadjuvant bevacizumab q2weeks and temozolomide using a 5/28 days regimen (BT-regimen) or bevacizumab q2weeks and irinotecan q2weeks (BI-regimen) for 28 days. All patients then received standard concomitant radiotherapy (60 Gy/30 fractions) combined with the BT or BI regimen as described; however, in the BT arm, temozolomide was administered daily ad modum Stupp during radiotherapy. Following radiotherapy, adjuvant BT was continued for 6 months in the BT arms. Response was assessed by MRI (WHO bidimensional measurements) and MGMT promoter status. Toxicity was assessed by CTCAE 3.0. The study was subsequently reviewed by an expert neuroradiologist who was blinded to treatment. 63 patients were included. The median age, performance status (0/1/2), and sex (male/female) in the BI/BT arms were 59/62, (20/10/1), 1/13/17 (2), and 18/13/21 (1/1), respectively. Responses at 8 weeks in the BI/BT arms were: complete response 0, partial response 10, 10, 10.
minor response (25-50% reduction compared to baseline) 7/11, no change 7/6, and progressive disease 6/4. Five patients on the BI-regimen and one on the BT-regimen were non-evaluable at 8 weeks: 4 had non-enhancing regimen. Response at 8 weeks seemed to favor the BT regimen and seemed to support current investigations of adding bevacizumab to Stupp’s regimen in first-line therapy. Updated secondary endpoints will be available by November 2011

NO-48. SAFETY AND ACTIVITY OF INTRA-CSF TRASTUZUMAB IN PATIENTS WITH NEUROPLASTIC MENINGITIS FROM BREAST CANCER OR PRIMARY BRAIN TUMORS
Omar Zalatimo, Cody Weston, Christina Zoccoli, and Michael Glantz; Penn State Hershey Medical Center, Hershey, PA

OBJECTIVE: To establish the safety and activity of intra-CSF trastuzumab in patients with neoplastic meningitis from breast cancer or malignant primary brain tumors.

BACKGROUND: Neoplastic meningitis is a devastating complication of extra-CNS malignancies and primary brain tumors with few available treatments. Trastuzumab, a large-molecule monoclonal antibody directed against the HER2/neu receptor (overexpressed on some breast cancers, glioblastomas, and medulloblastomas) has negligible access to the CSF after intravenous administration. Intra-CSF administration could circumvent this barrier. METHODS: Seven patients with neoplastic meningitis (4 GBM, 2 breast cancer, 1 medulloblastoma) and progressive neurologic deterioration were treated with intra-CSF trastuzumab (20-60 mg per dose, either weekly or every other week) for four treatments. Age ranged from 29 to 68 (median 53) years; KPS ranged from 70 to 90 (median 80). Patients who were neurologically stable or improved after four treatments were continued in therapy every other week until neurologic progression. CSF cytology, neurologic status, and KPS were assessed at each treatment. HER2/neu status of the primary tumors was also evaluated. RESULTS: One of the 2 patients with breast cancer (both HER2/neu+/+) and one of 3 patients with GBM (all 3 HER2/neu+/+) continued to respond clinically and cytologically 4 and 14 weeks after initiating treatment. The patient with medulloblastoma (also HER2/neu+/+) continues to respond clinically and cytologically after 5 weeks. Seven of 11 patients with GBM have responded (2 cytologically, all 7 clinically) with response durations ranging from 9 to 12+ weeks. HER2/neu status was assessed. There were no adverse events related to the trastuzumab. CONCLUSIONS/RELEVANCE: Trastuzumab can safely be administered into the CSF in patients with solid tumor neoplastic meningitis. Sustained clinical and cytologic responses may occur in patients with breast cancer and primary brain tumors. HER2/neu status may predict response. Further study to establish the biologically optimum dose and efficacy of this agent may be warranted.

NO-49. USING-ADC/CBV RATIO AS A POTENTIAL IMAGING BIOMARKER TO CHARACTERIZE RESIDUAL/RECURRENT METASTATIC TUMOR FOLLOWING RADIATION THERAPY
Syed Rahmanuddin, Mark S. Shiroishi, Steven Y. Cen, Jesse Jones, Thomas Chen, Paul Pagnini, John Go, Alex Lerner, Jessica Gomez, and Meng Law; University of Southern California, Los Angeles, CA

We sought to explore the use of a ratio between ADC values and maximum relative cerebral blood volume as a potential biomarker to diagnose residual or recurrent metastatic tumor from radiation necrosis following radiation therapy. In this retrospective study, we included 8 patients who were treated with radiation therapy for metastatic brain tumor and underwent conventional diffusion-weighted, diffusion-tensor MR imaging, all T2*-weighted dynamic susceptibility contrast MR imaging. Primary malignancies included breast, renal cell, lung, and testicular carcinoma. 3 patients developed increase in the size of the enhancing lesion on follow-up imaging, which is concerning for radiation necrosis or residual or recurrent tumors. 5 patients were found to have stability or decrease in the size of enhancing lesions on follow-up. The follow-up period ranged between 3-32 months. Regions of interest were drawn within the contrast-enhancing regions for ADC analysis. To derive maximum relative cerebral blood volume of the enhancing lesion, color maps were used to guide placement of ROIs in the lesion. This was normalized to normal-appearing white matter. The 3 patients with increased enhancement on follow-up imaging were found to have residual or recurrent tumor at surgery. The 3 patients with stable or decreased enhancement were assumed to be successfully treated. There appeared to be a negative correlation between ADC and rCBV max for all patients. For patients assumed to be successfully treated, the ADC/rCBV max ratio was essentially double the value of those associated with residual or recurrent tumor. Our preliminary work suggests that an ADC/rCBV max ratio may be able to distinguish residual or recurrent tumor. Although no cases of pathologically confirmed radiation necrosis were found in those with increase in the size of enhancement, there appeared to be a potential difference between confirmed residual or recurrent tumor cases and those that appeared to be successfully treated. We feel that further study utilizing these metrics in a larger study population is warranted.

NO-50. COMPARING THE EFFECT OF NOVOTTF TO BEVACIZUMAB IN RECURRENT GBM: A POST-HOC SUB-ANAHLYSIS OF THE PHASE III TRIAL DATA
Zori Ramji, Eric T. Wong, and Philip H. Gutin; Tel Aviv Medical Center, Tel Aviv, Israel; 2BIDMC, Boston, MA; 3MskCC, NYC, NY

BACKGROUND: NovoTTF-100A (Novocure Ltd) is a portable device that uses disposable scalp electrodes to deliver low intensity, alternating electric fields that interfere with cell division. The device has recently been approved by the FDA for the treatment of recurrent GBM based on data from a phase III study in recurrent GBM. Bevacizumab (Avastin) is FDA-approved based on non-controlled data for the treatment of the same condition. This presentation will describe a post-hoc subanalysis of the phase III data comparing the outcome of patients randomized to receive either NovoTTF or bevacizumab in the ITT population. METHODS: 237 adalimumab or enrolled in GBM randomized to receive in the US and Europe and assigned to receive either NovoTTF-100A (TTF, n = 120) administered continuously or the best available chemotherapy at the physician’s discretion (BAC, n = 117). Of the 117 BAC patients, 36 had received bevacizumab alone or in combination with a cytotoxic chemotherapy. Patient characteristics in both TTF and bevacizumab groups were well balanced for age, KPS, recurrence number and prior surgical resections. Baseline tumor size was slightly smaller in TTF patients (14.5 vs. 15.3 cm²). TTF patients were 19.1% and TAC patients 11.1% who failed bevacizumab prior to enrollment. Overall survival (OS) served as the primary endpoint, and PFS6 and 1-year survival were used as secondary endpoints. RESULTS: Overall survival in the ITT population was higher in TTF compared to bevacizumab patients (median 6.6m vs. 5.0m, respectively; p < 0.054; HR = 0.65). A Cox proportional hazards model showed this difference to be statistically significant (p = 0.048; HR = 0.65; 95%CI 0.51-0.90). 1-year survival in TTF patients was 22% vs. 14% in bevacizumab patients. PFS6 was 21% in both groups. CONCLUSIONS: This post-hoc analysis suggests a superior OS in TTF patients compared to patients who received bevacizumab. A randomized clinical trial should be performed to confirm the validity of this observation.
NO. 52. PET-FET POSITIVE BRAIN LESIONS: A COMPARISON OF 18F-FET-PET, MRI, AND HISTOPATHOLOGICAL FINDINGS

Nowosielski Martha, Schweitz Jacqueline, Gotwald Thaddaeus, Putzer Daniel, Maier Hans, Muigg Armin, Trinka Eugen, Stockhammer Günther, Markus Hutterer, Medical University Innsbruck, Innsbruck, Austria; Paracelsus Medical University Salzburg, Salzburg, Austria

BACKGROUND: Because of the high incorporation rate of the labeled amino-acid 18F-fluoroethyl-L-tyrosine (18F-FET) into glioma cells 18F-FET-PET is increasingly used for diagnosis, treatment planning, and monitoring of therapy. The specificity of 18F-FET-PET for brain tumors, however, is still unknown. METHODS: We retrospectively analyzed 815 18F-FET-PET-scans from 391 patients using Standard-Uptake-Value calculations (SUVmax, SUVmean) and compared the results with MRI and/or histopathological findings. Using ROC curve analysis, we calculated the optimal SUV threshold value for a 18F-FET positive lesion. RESULTS: The optimal threshold value for absolute 18F-FET SUV was determined with 2.0 (sensitivity and specificity were 80% and 85%, respectively). Many lesions were found to be hypermetabolic on 18F-FET-PET, including astro- and oligodendrogial tumors (= glioma group; n = 261 patients / 685 scans), other benign and malignant primary brain tumors (pilocytic astrocytoma WHO I, ependymoma WHO II-III, PNET / medulloblastoma / pinealoma WHO IV, Primary CNS Lymphoma WHO IV, ependymomas, acoustic neuroma, meningioma WHO I/II, tumor like-lesions (DNET, ganglioglioma, cavernoma), and active inflammatory (MS, ADEM, encephalitis), subacute ischemic (sinus vein thrombosis), and traumatic lesions (= non-glial lesion group; n = 130 / 130 scans). In glioma patients 18F-FET-PET was able to identify hot spots of higher malignancy for surgery planning as well as post-surgery residual tumor burden for radiotherapy planning better than MRI. In addition, in the course of temozolomide and bevacizumab chemotherapy, 18F-FET-PET was helpful to discriminate between pseudoprogression / pseudoresponse and real tumor progression. CONCLUSIONS: 18F-FET-PET hypermetabolism is detectable in various neoplastic, inflammatory, ischemic, and traumatic brain lesions, which limits the specificity of this method to identify tumors as gliomas. In patients with gliomas 18F-FET-PET represents a helpful method for surgery and radiotherapy planning as well as for chemotherapy treatment monitoring.

NO. 53. CENTRAL NEUROCYTOMA: TRANSULCUS APPROACH FOR TOTAL EXCISION

Ham-Min Tseng; National Taiwan University Hospital, Taipei, Taiwan

Central neurocytoma is a rare intraventricular tumor. The origin of the tumor is believed from the septum pellucidum. In MRI images, it is heterogeneous, and some part shows low enhancement. During the past 5 years, 12 patients with central neurocytoma were treated. Two image-diagnosed tumors were incidentally found during general health examination. Surgery was refused, and they received follow-up only. Slow growth was found in these two patients during 9 months and 2 years after diagnosis. A trans-ulcus approach was chosen to excise the large tumors (over 4.5 cm), and total excision was achieved in 8 patients. A small piece of tumor was left in a patient with an 8 cm long tumor. Only one tumor was excised through a transcrosal approach. One patient had tumor extending from right lateral ventricle through foramen Monro, third ventricle, and the aqueduct into fourth ventricle. It was removed without any neurological sequelae. Two patients had postoperative hemiparesis due to a basal ganglia infarct. One recovered after 6 months of rehabilitation. All of these tumors received abundant vascular supply from the thalamus. The early devascularization of blood supply from the thalamus and complete visualization of the tumor (especially the under surface of corpus callosum) for easier total excision are the reasons the author preferred the trans-ulcus approach. There was no recurrence during the short follow-up (less than 5 years). The advantages and disadvantages of transcrosal and trans-ulcus approach will be discussed.

NO. 54. INADVERTENT UNDERDOSEING OF PATIENTS WITH NEOPLASTIC MENINGITIS: SHOOTING TO KILL OR GETTING SHOT IN THE FOOT

Christina M. Zosoli, Michael Glantz, Omar Zalatimo, Akshal Patel, Kathleen Rizzo, and Jonas M. Sheehan; Penn State College of Medicine, Hershey, PA

INTRODUCTION: The mainstay of treatment for patients with neoplastic meningitis (NM) is intra-CSF chemotherapy administered through a ventricular reservoir. Numerous administration strategies have been advocated in the literature and are used in practice. This wide variation in practice suggests uncertainty regarding the optimal approach. Measuring the amount of radionuclide remaining in the delivery syringe, the butterfly tubing and needle, and the reservoir itself during the performance of CSF flow studies may provide data relevant to the efficacy of drug delivery. METHODS: Twenty patients with NM underwent conventional CSF flow studies using indium-111 DTPA. Four administration techniques that reflected published recommendations were used: 0.4 ml of radioisotope-barbotaged with 10 ml of autologous CSF (2 patients); 3 or 5 ml of radioisotope-barbotaged with 10 ml of CSF (3 and 4 patients, respectively) or not barbotaged but followed by repeated reservoir bulb compression (4 patients each); and 5 ml of radioisotope diluted with 5 ml of CSF, injected, and followed by repeated reservoir bulb compression (3 patients). Residual radionuclide counts were measured in the injection syringe, buttry needle apparatus, and reservoir bulb. RESULTS: A substantial fraction of the injected dose remained in the reservoir bulb whenever a CSF flush was not used (mean 17.1%, range 8.6 - 57%) compared with a mean of 1.7% (range 0.44 - 3.1%) for all cases using a CSF flush (mean difference 15.4%, SE 3.5 ± 25.5, p ≤ 0.0049). Residual radionuclide in the syringe and butterfly was negligible (≤ 1%) in all cases. CONCLUSION: Many patients with NM are being inadvertently and substantially underdosed when receiving intra-CSF chemotherapy through a ventricular reservoir. Optimum administration requires placing drug in a total volume of 3-5 ml and barbotage with 10 ml of autologous CSF.

NO. 55. CHEMORADIATION-INDUCED THROMBOCYTOPENIA IMPACTS MORBIDITY AND MORTALITY IN NEWLY-DIAGNOSED HIGH-GRADE GLIOMA PATIENTS

Ashley L. Sumrall, James J. Vredenburgh, Annick Desjardins, David A. Reardon, Henry S. Friedman, and Katherine B. Pears; Duke University Medical Center, Durham, NC

Although the literature points to <5% of high grade glioma (HGG) patients suffering from chemoradiation-induced thrombocytopenia, little is understood about how this side effect can impact treatment trajectory and survival. Since 2003, concurrent chemoradiation with temozolomide (TMZ) followed by dose-dense TMZ for 6 to 12 months has become the standard of care for WHO grade III/IV newly diagnosed gliomas. Current clinical recommendations advise interruption of therapy if thrombocytopenia develops. Using a retrospective design, we conducted a single-center chart review to evaluate patients with HGG who have developed thrombocytopenia (defined as a platelet count of less than 100 x 10⁹/L) while receiving concurrent TMZ and radiation therapy either on or off clinical trials at the Preston Robert Tisch Brain Tumor Center at Duke from November 2007 until December 2010. A control group of patients undergoing similar therapy for HGG was randomly selected for comparison. Particular attention was given to time of onset and duration of thrombocytopenia, median platelet count nadir, platelet transfusion requirements, progression-free survival (PFS), and overall survival (OS). In our cohort of 20 thrombocytopenic patients, all experienced interruption or cessation of chemotherapy due to thrombocytopenia, and at present, they had a median PFS of 9.8 months and OS of 11.1 months. Currently, the control group who received fully-scheduled chemoradiation therapy experienced a median PFS of 11.6 months and OS of 12.0 months. In the cohort of thrombocytopenic patients, the median platelet count nadir was 21 x 10⁹/L (range 2 to 85 x 10⁹/L). Median duration of the nadir was 14.5 days. 9 of 20 patients (45%) required at least 2 platelet transfusions during this time. Further research is warranted to understand morbidity and mortality in this population associated with thrombocytopenia and to investigate possible methods of intervention.
NO.57. CARCINOMATOSIS MENINGITIS ASSOCIATED WITH SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK

Nicholas A. Blondin1,2, Joachim M. Baehring3; Yale University School of Medicine, New Haven, CT

INTRODUCTION: Carcinomatosis meningitis is a serious complication of metastatic cancers and often causes significant neurologic morbidity. Although it is most often associated with breast cancer, lung cancer, melanoma, and gastrointestinal malignancies, it has rarely been reported in cases of squamous cell carcinoma of the head and neck. METHODS: We report the clinical, imaging and histopathologic features of two cases of carcinomatosis meningitis associated with squamous cell carcinoma of the head and neck and present the results of a comprehensive literature review. RESULTS: A 72-year-old man developed a skin lesion above his left eyebrow that was later diagnosed as squamous cell carcinoma. Six months after diagnosis, he developed left forehead numbness, left abducens palsy, and left facial nerve palsy. MRI demonstrated thickening and enhancement of the affected cranial nerves, but CSF cytology did not reveal any malignant cells. He was treated with systemic cetuximab, carboplatin, and methotrexate as well as intrathecal thiopeta and focal radiation therapy. Two years after diagnosis, his carcinomatosis meningitis remains stable. A 67-year-old man developed a skin lesion on his left cheek that was subsequently diagnosed as squamous cell carcinoma. Three years later, he developed left facial numbness and weakness, and MRI demonstrated thickening and enhancement of the trigeminal and facial nerves. A biopsy demonstrated perineural involvement by carcinoma, but repeated lumbar punctures were negative for malignancy. He was treated with cetuximab, carboplatin, fluorouracil, and focal radiation therapy. His carcinomatous meningitis later spread to involve multiple nerve roots. He died at ten years after diagnosis because of progression of disease. CONCLUSIONS: Carcinomatous meningitis is a rare complication of squamous cell carcinoma of the head and neck. Cephalic suspicion and imaging can support the diagnosis, and cytology of the CSF may be falsely negative. Biopsy can provide definitive diagnosis. Systemic and intrathecal chemotherapy, as well as radiation therapy, can be used as treatment.

NO.58. OUTCOMES IN PEDIATRIC AND ADULT CENTRAL NERVOUS SYSTEM (CNS) Primitive Neuroectodermal Tumors (PNET)

Tyler Foote, Nadia Laack, and Jason Call; Mayo Clinic, Rochester, MN

PURPOSE: To compare outcomes for adult and pediatric patients treated for central nervous system (CNS) primitive neuro-ectodermal tumor (PNET) at a large academic center. METHODS: 25 patients with a diagnosis of PNET were retrospectively reviewed. Median age was 20. 14 patients were adults at diagnosis (age > 18). 21 PNETs were located in the brain, and 4 were elsewhere in the CNS (spine or meninges). All patients were staged with an MRI; 20 had an MRI of the spine for staging. 17 patients had M0 disease, 1 had M1 disease, and M status was unknown in 2 patients. All patients had biopsy. Only 5 had subtotal resections, 13 had gross total resections, and 1 had no surgery of the primary tumor. 12 patients were classified as high risk, 13 as standard risk, 21 received chemother- apy. All but 1 patient received intrathecal cytarabine through an Ommaya reservoir and has been on intrathecal cytarabine through an Ommaya reservoir and has been treated with adriamycin and cytoxan X 4 cycles followed by taxotere and XRT to the chest wall and regional lymphatics followed by 3 years of tamoxifen. She was then NED for 3 years when lesions were estimated with PET-Scan Meier survival associated with this patient. Ventilation requiring intubation for poor oxygen saturation. Spinal fluid was cloudy with a glucose of 42, elevated protein of 175, 32 white cells, 18 red cells. She was negative for West Nile virus and Lyme disease by rapid PCR. Her opening pressure was 280 cm. She was discharged without a diagn- osis and for the next year had a recurrent symptom complex of drop attacks, severe tinnitus, muffled hearing, and diplopia. After 12 months, she developed papilledema in her left eye. PET scan showed no systemic spread to involve multiple nerve roots. He died at ten years after diagnosis of disease.

NO.59. TREATMENT OUTCOME FOR 757 PATIENTS WITH GLOBLASTOMA IN 3 POPULATION-BASED NEURO-Oncology CENTRES

Mark G. Hamilton1, Simon Walling2, Misha Eljasz1, and Jay Easaw1; 1University of Calgary, Calgary, AB, Canada; 2Dalhousie University, Halifax, NS, Canada

INTRODUCTION: Patients with glioblastoma multiforme (GBM) have historically had a median survival of 9-11 months after surgery and radiation therapy (RT). The addition of temozolomide (TMZ) to standard of care was supported by the 2005 Stupp study, which reported a median survival of 14.6 months. However, variation exists between and within patient populations. We examined 3 geographically distinct patient populations and evaluated the role of various prognostic factors. METHODS: Patients with GBM were identified at three Canadian centers in two Canadian provinces from prospectively collected databases of population-based neuro-oncology centers (years 2001-2008). Biopsy or extensive surgical debulking of the tumor was undertaken followed by RT, or RT with concomitant TMZ followed by 6 cycles of TMZ. MGMT promoter methylation status was assessed when possible. RESULTS: A total of 757 patients were analyzed from three centers: Calgary (n = 352), Edmonton (n = 211), and Halifax (n = 194). The mean age was 60 years, 64% were male, and the overall median survival was 9 months with no difference among sites (p = 0.90). The median survivals for methylated (n = 172) versus other methylation statuses (n = 585) was 12 versus 8 months, for debulking (n = 485) versus biopsy (n = 272) was 11 versus 5 months, and for RT + TMZ (n = 421) versus otherwise (n = 334) was 13 versus 4 months; p < 0.001. A wider gradient of median survivals was achieved by assigning a value of 1 for each of methylated, debulking, and RT + TMZ treatment and summing to a score between 0 and 3. The median survivals for patients scoring 0 (n = 135), 1 (n = 254), 2 (n = 278), and 3 = 90) were 3, 7, 12, and 19 months, respect- ively. CONCLUSION: Interpreting similar methylation status data across the three centers, yet patient outcomes (median survival) were very com- parable. Patients undergoing surgical debulking of methylated tumors who had both radiation therapy and chemotherapy had the best median outcome (median survival 19 months).

NO.60. MOLECULAR SUBTYPING OF MEDULLOBLASTOMAS: INDIAN SCENARIO

Neelam V. Shirsat1, Ratika Kundar1, Amit Gokhale1, Atul Goel2, and Ali A. Asaad3; 1University of Calgary, Navi Mumbai, India; 2Seth G. S. Medical College & K.E.M. Hospital, Mumbai, India

MicroRNA (miRNA) profiling of 19 medulloblastomas and four normal cerebellar tissues was carried out using a Taqman Low Density array v 1.0 which assesses 365 human miRNAs. In parallel, genome-wide expression profiling of protein coding genes was carried out using Affymetrix gene 1.0 ST arrays. Both profiling studies segregated medulloblastoma tumor tissues into four nearly identical molecular subtypes whereas normal cerebel- lar tissues segregated into a distinct group. A total of 43 medulloblastomas were analyzed for the expression of a select set of marker genes and published often significantly differentially expressed in the four molecu- lar subtypes. Twelve out of 43 medulloblastomas in our study were found to carry mutations in the CTNNB1 gene, which led to WNT pathway activa- tion. Median age at diagnosis for WNT signaling-associated medulloblas- tomas is reported to be higher than that for all medulloblastomas. Median age at diagnosis of WNT signaling-associated tumors in our data is
NO.61. TUMOR-ASSOCIATED GLIAL CELLS PROMOTE GROWTH OF GBM XENOGRAPHS IN EGFP NO-64. TRIPLE-NEGATIVE LOW-GRADE GLIOMAS: A HIGHLY AGGRESSIVE TUMOR WITH DISMAL PROGNOSIS

INTRODUCTION: The FDA-approved schedule and dose of bevacizumab (BVZ) for recurrent glioblastoma (rGB) (10 mg/kg q 2 weeks) were adopted arbitrarily from certain colon cancer protocols. No dose defining studies have been performed for GB. We began using BVZ for treatment of rGB in 2005 at 5 mg/kg q 2 weeks combined with irinotecan and in the last 2 years as a single agent at the same dose. Our previous report of 20 patients treated with BVZ 5 mg/kg q 2 weeks showed similar response rate and overall survival (OS) to other BVZ treatment protocols with less adverse effects. In this study, we retrospectively reviewed our 6-year experience with BVZ in 125 rGB patients. OBJECTIVE: To compare treatment outcomes for BVZ doses of 5 mg/kg vs. 10 mg/kg. PATIENTS: 90 patients received BVZ at 5 mg/kg and 35 patients at 10 mg/kg. Median KPS and age were similar in both groups. There was a trend for prolonged survival for the higher dose (290 vs. 192 days; p = 0.451). Median OS was similar for groups treated with BVZ monotherapy at any dose vs. combined chemotherapy (211.5 vs. 220 days; p = 0.455). Further analysis of the incidence of adverse effects in the respective subgroups will be reported. CONCLUSION: There is no significant difference in OS for rGB treated with BVZ doses of 5 mg/kg vs 10 mg/kg. The higher dose regimen was associated with a trend for prolonged OS. The addition of cytotoxic agents to BVZ did not result in prolongation of OS.

NO.64. TRIPLE-NEGATIVE LOW-GRADE GLIOMAS: A HIGHLY AGGRESSIVE TUMOR WITH DISMAL PROGNOSIS

Metellus Philippe1, Carin Colare2, Maues de Paula Andre1, Barrie Marylin1, Chonot Olivier1, Ouaffik L'houcine1, and Figarella-Branger Dominique2; Timone University Hospital, Marseille, France; CRO2 INSERM U911 Timone University of Medicine, Marseille, France

BACKGROUND: The phenotypic heterogeneity of low-grade gliomas (LGGs) is still inconsistently explained by genetic alterations characteristic in patients treated according to present standards of care. Here we investigate the combined analysis of three molecular alterations according to clinical and radiologic data in a series of 89 LGGs to provide new insights into LGG pathogenesis. METHODS: IDH1 codon 132 and IDH2 codon 172 sequencing was performed in a series of 89 LGGs and correlated with clinical presentation, MR imaging characteristics, genomic profile, and outcome. Furthermore, p53 expression and 1p19q deletion status was assessed in all cases. RESULTS: A total of 74 IDH1 mutations at codon 132 and 2 IDH2 mutations at codon 172 were found. There were 13/22 patients with a better outcome (5-year survival rate, 91% v. 54%, respectively, P < 0.001 when compared to samples without IDH1 mutations. After adjustment for age, tumor location and size, radiologic infiltration pattern, and extent of surgery, multivariate analysis confirmed that the presence of IDH1 mutations was an independent favorable prognostic factor (hazard ratio: 34.6; 95% CI, 2.72 to 329.32; P = 0.006). Furthermore, we showed that patients treated with bevacizumab 10 mg/kg d 1 and 15 q28 until progression disease or, unacceptable toxicity in combination with temozolomide 150 mg/m2 q week on-week off for 6 cycles. The primary endpoint of the study was progression-free survival (PFS). The toxicity was similar to that reported in the phase II metronomic schedule. The aim of this study was to identify cancer-related genes associated with the treatment effect in GB. The recruitment of the host vasculature and the infiltrative behaviors of gliomas underscore the significance of tumor-stroma interactions in brain tumor pathogenesis. The aim of this project was to identify cancer-related genes associated with the treatment effect in GB.

NO.62. PHASE II STUDY OF BEVACIZUMAB IN COMBINATION WITH DOSE-DENSE TEMOZOLOMIDE IN PATIENTS WITH RECURRENT GROWTH OF GBM XENOGRAPHS IN EGFP NO-64. TRIPLE-NEGATIVE LOW-GRADE GLIOMAS: A HIGHLY AGGRESSIVE TUMOR WITH DISMAL PROGNOSIS

Analysis: Juan Sepulveda1, Cristobal Belda2, Carmen Balanía1, Pedro Perez Segura3, Anselmo Reyrozo4, Miguel Gil5, Oscar Gallego6, and Alfonso Berrocal1; 1Hospital de la Princesa, Madrid, Spain; 2Hospital Germans Trias i Pujol, Badalona, Spain; 3Hospital Clinico San Carlos, Madrid, Spain; 4Hospital Universitari i Politècnic La Fe, Valencia, Spain; 5Hospital Sao Carlos, Madrid, Spain; 6Hospital Universitari i Politècnic La Fe, Valencia, Spain

Glioblastoma (GB) is among the most aggressive malignant brain tumors in the adult population. In recurrent GB, bevacizumab with irinotecan has been used as a single agent in phase II clinical trials; the combination has reported a significant improvement of RR, 6 month progression-free survival (FP56), and PFS (150 mg/m2 q 2 weeks). There are limited data on safety of bevacizumab in combination with other widely used chemotherapy agents such as temozolomide. The aim of this study is to evaluate the efficacy and safety of the combination of bevacizumab and dose-dense temozolomide. We report the safety profile of the first 10 patients treated in a Spanish phase II multicenter, open-label study in patients with recurrent GB treated with bevacizumab 10 mg/kg d 1 and 15 q28 until progression disease or, unacceptable toxicity in combination with temozolomide 150 mg/m2 q week on-week off for 6 cycles. The primary endpoint of the study was progression-free survival (PFS). The toxicity was similar to that reported in the phase II metronomic schedule. The aim of this study was to identify cancer-related genes associated with the treatment effect in GB. The recruitment of the host vasculature and the infiltrative behaviors of gliomas underscore the significance of tumor-stroma interactions in brain tumor pathogenesis. The aim of this project was to identify cancer-related genes associated with the treatment effect in GB.
with tumors that lacked IDH mutations were significantly older (P < 0.05) and that these tumors involved significantly more frequently the insula (P < 0.05), were larger in size (≥6 cm, P < 0.05), displayed an infiltrative growth pattern (P < 0.05), and were associated with a 1p19q deletion (P < 0.05). CONCLUSIONS: The combined absence of IDH mutations, p53 expression and 1p19q co-deletion in LGGs identifies a novel entity coined “Triple negative” tumors with distinctive location, infiltrative growth pattern, distinct molecular alterations and dismal outcome. These findings could significantly modify LGG classification and may represent a new tool to guide patient-tailored therapy.

NO-65. PROGNOSTIC SIGNIFICANCE OF MGMT PROMOTER METHYLATION STATUS IN ELDERLY PATIENTS WITH NEWLY DIAGNOSED GLIOBLASTOMA: THE BENEFIT OF BCNU WAFER IMPLANTATION: A PROSPECTIVE PATIENT COHORT

BACKGROUND: The optimal treatment for elderly patients (age ≥ 70 years) with glioblastoma (GBM) remains controversial. A recent randomized study conducted on newly diagnosed GBM patients demonstrated that concomitant and adjuvant temozolomide added to standard radiotherapy had a survival advantage compared with radiotherapy alone. The overall survival benefit of this aggressive treatment, however, was attenuated in older or patients with poor performance status. We assessed a prospective cohort of elderly patients (age ≥ 70 years) with GBM treated with BCNU wafer implantation and we explored MGMT methylation status correlation with clinical outcome. METHODS: Newly diagnosed GBM patients (age ≥ 70 years) were considered eligible. Treatment consisted in surgical resection with BCNU wafer implantation in all cases. Adjuvant radiotherapy was performed in 29 patients. MGMT methylation status was determined by a high-throughput quantitative methylation assay. The relationship between MGMT methylation status and survival was assessed with regard to other recognized prognostic factors. RESULTS: Median overall survival (OS) among the 31 patients was 12 months (95% CI: 6.8-17.2). The 6-month and 12-month OS rates were 58% and 21%, respectively. For age and KPS, patients with age ≥ 70 years and KPS ≥ 70 showed better survival (P < 0.05) and MGMT hypermethylation (P < 0.001), and age ≥ 80 (P = 0.041) were independently associated with a better OS. CONCLUSIONS: MGMT methylation status is an important prognostic factor in elderly patients treated with surgery plus BCNU wafer implantation for GBM and therefore is useful in predicting the outcome of GBM in this population.

NO-66. MULTIFOCAL INTRADURAL MENINGEAL METASTASIS ASSOCIATED WITH PILOCYTIC ASTROCYTOMA

Pilocytic astrocytoma or cystic cerebellar astrocytoma is predominately identified in young children and adults under the age of 20. Pilocytic astrocytoma is classified by the World Health Organization as a grade-1 benign tumor. By definition a low-grade astrocytoma involving primarily the cerebellum, pilocytic astrocytoma may occur in other midline areas of the neuroaxis including the brainstem, third ventricle, hypothalamus, sellar region, optic chiasm, and rarely, the spinal cord. The most common symptoms on presentation are headache and seizure. Neurologic examination may reveal papilledema, gait ataxia, and hemiparesis. Less common findings include cranial nerve palsies, dysphagia, and behavioral changes. We report a 54-year-old Caucasian female who developed left facial numbness after receiving a local injection to his lower lumbar region after an automobile accident. Initially a diagnosis of maxillary sinusitis was the cause of his facial numbness, and he was prescribed a course of antibiotics. After his symptoms failed to resolve, an MRI of his brain was performed. MRI of the brain demonstrated abnormal density in the suprasellar cistern that appeared to contact the optic chiasm. Lumbar puncture revealed elevated opening pressure of 450 mm H2O without evidence of malignancy in the cytology. Fundus examination demonstrated a normal optic disc. He underwent ventriculoperitoneal shunting that improved his papillledema but failed to relieve his intermittent dizziness and increased lower lumbar pain that radiated to his right leg. Follow-up MRI of the brain and total spine revealed meningial thickening from the cerebellopontine cistern and distal to the lumbar puncture site. Subsequent ventriculoperitoneal shunting was performed in an attempt to relieve bilateral papilledema and ventriculomegaly. Since initial presentation, she has undergone re-resection after a surveillance MRI revealed interval progression of the fourth ventricle mass despite radiation and chemotherapy. Pathologic specimens returned findings consistent with recurrent pilocytic astrocytoma without more malignant features noted.

NO-67. MULTIFOCAL INTRADURAL MENINGEAL METASTASIS ASSOCIATED WITH PILOCYTIC ASTROCYTOMA

Michael A. Errico and Lara J. Kunschner; Allegheny General Hospital, Pittsburgh, PA

Pilocytic astrocytoma or cystic cerebellar astrocytoma is predominately identified in young children and adults under the age of 20. Pilocytic astrocytoma is classified by the World Health Organization as a grade-1 benign tumor. By definition a low-grade astrocytoma involving primarily the cerebellum, pilocytic astrocytoma may occur in other midline areas of the neuroaxis including the brainstem, third ventricle, hypothalamus, sellar region, optic chiasm, and rarely, the spinal cord. The most common symptoms on presentation are headache and seizure. Neurologic examination may reveal papilledema, gait ataxia, and hemiparesis. Less common findings include cranial nerve palsies, dysphagia, and behavioral changes. We report a 54-year-old Caucasian female who presented with complaints of headache, neck stiffness, and increased lower lumbar pain that radiated to his right leg. Follow-up MRI of the brain and total spine revealed meningial thickening from the cerebellopontine cistern and distal to the lumbar puncture site. Subsequent ventriculoperitoneal shunting was performed in an attempt to relieve bilateral papilledema and ventriculomegaly. Since initial presentation, she has undergone re-resection after a surveillance MRI revealed interval progression of the fourth ventricle mass despite radiation and chemotherapy. Pathologic specimens returned findings consistent with recurrent pilocytic astrocytoma without more malignant features noted.
pulmonary embolism). CONCLUSION: BV + FTM in glioblastomas that recur after standard treatment is safe and promising. MGMT methylation data will be presented.

NO-69. AN OPEN LABEL, PROSPECTIVE, MULTICENTRIC STUDY TO EVALUATE THE SAFETY AND EFFICACY OF NIMOTUZUMAB INDUCTION AND MAINTENANCE THERAPY IN COMBINATION WITH RADIOTHERAPY PLUS TEMOZOLOMIDE (CONCOMITANT & ADJUVANT) IN INDIAN PATIENTS WITH GliOblastoma MultiFOrMe Rakesh Jali1, P.K. Julla2, A.K. Anand3, Devang Bhavsar4, Neetu Singhal3, Radheyshyam Naik5, Subhasini John6, and Beela S. Mathew8; 1Tata Memorial Hospital, Mumbai, India; 2HIMC, DELHI, India; 3Max Hospitals, Delhi, India; 4GCRI, Ahmedabad, India; 5Dharmsilla Hospital, New Delhi, India; 6HCG Hospitals, Bangalore, India; 7CMC, Vellore, India; 8RCC, Trivandrum, India

AIM: To evaluate the safety and efficacy of nimotuzumab (BIOMAb-EGFR) in combination with temozolomide and radiotherapy in glioblastomas. METHODS: Patients were accrued in an open-label, prospective, multicentric study for patients with glioblastoma. 56 suitable patients underwent from 5 centers of treatment: chemotherapy, radiation, and extended maintenance. Temozolomide (TMZ) was given 75 mg/m² daily for six weeks along with the study drug nimotuzumab in concurrent stages. Radiotherapy was given daily at 1.8 to 2 Gy per fraction five days a week for six weeks. The study showed that adding nimotuzumab to the standard of care (radiotherapy plus TMZ) appears to be encouraging in terms of OS for patients with newly diagnosed GBM.

NO-70. EPSTEIN-BARR VIRUS (EBV)-DRIVEN CENTRAL NERVOUS SYSTEM LYMPHOMA (CNSL) Ivayai Thaipisuttikul, Jerome Graber, and Lisa M. DeAngelis; Memorial Sloan-Kettering Cancer Center, New York, NY

We report 11 patients with positive CSF EBV PCR who were diagnosed with primary central nervous system lymphoma (PCNSL) and secondary CNSL from January 2000 to October 2010. Seven had PCNSL and 4 had secondary CNSL. Six patients (55%) were <18 years of age at diagnosis. Median age was 46 months (range 3-180 months) for PCNSL and 42 years (range 19-76 years) for secondary CNSL. All PCNSL patients had par enchymal brain disease; 5 had biopsy-confirmed DLBCL. 1 had kappa clonal excess on CSF flow cytometry, and 1 had clonal rearrangement of the immunoglobulin heavy chain gene in the CSF. All PCNSL patients had underlying immunosuppression. Overall survival rates were 56.9% at the end of 1 year and 26.3% at 2 years in the ITT population. Class IIB subjects showed an OS of 100% at 1 year and 62.5% at 2 years. Class IV subjects had an OS of 50% at 1 year and 11.5% at 2 years. Class V patients had an OS of 54.5% at 1 year and 21.9% at 2 years. Out of 59 total adverse events, the majority were mild (315) or moderate (190) in severity. There were 27 life-threatening events or events including disease progression, grade 4 toxicity, or death. Median time to progression of CNSL from diagnosis of PCNSL was 7 months (range 1-75 months) with 4 patients still alive. Of the 4 patients with secondary CNSL lymphoma, 1 had diffuse large B-cell lymphoma, 1 had composite marginal zone and mantle cell lymphoma, 1 had HTLV1-associated T-cell lymphoma, and 1 had Burkitt’s lymphoma. Patients had active systemic disease at CNS relapse. Three had parenchymal brain involvement, and the patient had lenalidomide and mescaline disease. Two patients were immunosuppressed (1 HIV and 1 allogeneic BMT) before the diagnosis of lymphoma. Three patients received non-methotrexate systemic chemotherapy with intrathecal methotrexate. One patient received temozolomide alone because of poor performance status. All 4 patients died with a median survival from diagnosis of CNSL relapse of 4 months (range 2-19 months). Two patients died of active CNS disease, one of active systemic disease, and one of neutropenic infection. EBV-driven lymphomas that involve the CNS have a worse prognosis than comparable EBV-driven lymphomas.

NO-71. INTEGRATED MOLECULAR PROFILING OF ADULT AND PEDIATRIC PILOCYTIC ASTROCYTOMA THROUGH SINGLE NUCLEOTIDE POLYMORPHISM ARRAY AND GENE EXPRESSION ANALYSIS

Margret Shirinian1, Adam M. Fontebasso2, Karine Jacob3, Noha Gerges4, Alexandre Montpetit5, Andre Nantel5, Steffen Albrecht6, and Nada Jabado7; 1Department of Human Genetics, McGill University, Montreal, QC, Canada; 2Division of Experimental Medicine, McGill University, Montreal, QC, Canada; 3McGill University and Genome Quebec Innovation Centre, Montreal, QC, Canada; 4Biotecnology Research Institute, National Research Council of Canada, Montreal, QC, Canada; 5Department of Pathology, Montreal Children’s Hospital, McGill University, Montreal, QC, Canada; 6Division of Hemato-Oncology, Department of Pediatrics and Human Genetics, Montreal Children’s Hospital, McGill University Health Centre, Montreal, QC, Canada

Pilocytic Astrocytoma (PA) is a Grade I Astrocytoma according to the WHO classification and is the most common brain tumor in children. Accounting for 23% of all pediatric brain tumors, PA occurs predominantly in infratentorial regions of the brain in pediatric patients and comprises about 80-85% of all tumors of the cerebellum in children. Recent studies have demonstrated key differences in the gene expression profiles of adult and pediatric glioblastoma multiforme (GBM), but molecular mechanisms important in PA tumorigenesis specific to adult and pediatric patients are largely uncharacterized. To address these questions, we genotyped and characterized the genetic characteristics of adult and pediatric PA tumors utilizing single nucleotide polymorphism (SNP) arrays. In addition, we used large-scale microarray-based gene expression profiling of adult and pediatric PA to characterize specific molecular mechanisms of importance in adult versus that of pediatric PA. Upon integration, gene expression profiles can be correlated with genomic alterations that may better profile PA tumors on the basis of patient age, neuroanatomical location, and genotype. We also demonstrated that PA tumors are characterized by frequent, complex, multigene rearrangements that may lead to distinct gene expression profiles, convolutional or consistent gene expression changes that distinguish PA with respect to age and brain location. We believe that integrated array-based analyses may allow us to more accurately profile adult and pediatric tumors and design more personalized patient therapy in clinic.
NO-73. TRIM11 IS A NOVEL AND SPECIFIC GLIOMA STEM-LIKE CELL MARKER THAT ALSO PLAYS A ROLE IN GLIOMA BIOLOGY THROUGH THE EGFR PATHWAY. Kajun Di, Mark Linskey, and Daniela A. Bota; UC Irvine, Orange, CA

SUMMARY: Expression of tripartite motif-containing protein 11 (TRIM11), a member of the TRIM/RBCC family of E3 ubiquitin ligases, is upregulated in high grade glioma-derived tumor stem-like cells (GSCs) while remaining low in glioblastoma multiforme (GBM) cell lines, low-grade glioma-derived GSCs, and normal neural stem/ progenitor cells (NSCs) studied in vitro. The expression pattern of TRIM11 strongly correlated with the stem cell markers CD133 and nestin in GSCs. Knockdown of TRIM11 inhibited proliferation, migration, and invasion of glioma cells and caused decreased EGFR levels and MAPK activity. These findings suggest that TRIM11 can be used to specifically identify and potentially target GBM-derived GSCs while selectively sparing normal NSCs and that TRIM11 also functions as an oncogene that promotes tumor growth and inva-

Significance: GSCs are important for tumor initiation, resistance to conventional therapies, and tumor recurrence after therapy. Unfortunately, all reported markers for identifying and potentially targeting these cells are shared in common with normal NSCs. Damage to normal NSCs resulting from glioma therapies can produce profound cognitive side effects. The potential to selectively identify and target GSCs while sparing NSCs is an important aim that may help to improve patient outcomes. Novel therapeutic strategies for malignan
t glioma with linkage into the EGFR signaling pathway expands our knowledge of TRIM11 biology and opens the door to exploring a potential new translational target for malignant glioma therapy. Highlights: 1) TRIM11 is up-regulated in high-grade glioma GSCs, but not in low-grade glioma GSCs and NSCs studied in appropriate in vitro conditions relative to their cell type. 2) The expression pattern of TRIM11 strongly correlates with that of CD133 and nestin in GSCs. 3) TRIM11 promotes the proliferation, migration, and invasion of malignant glioma cells. 4) TRIM11 modulates EGFR expression, possibly through regulating the transcription of HB-EGF

NO-74. IDH1 MUTATIONS IN GRADE II ASTROCYTOMAS ARE ASSOCIATED WITH UNFAVORABLE PROGRESSION-FREE SURVIVAL AND PROLONGED POST-RECURRENT SURVIVAL. Nikhil Chaturvedi, Elizabeth R. Eigenbrodt, Simonetta Jung, Joerg-Christian Tonni, Hans Kretzschmar, Aurelia Peraud, and Friedrich-Wilhelm Kreth; 1University Hospital Grosshadern, Munich, Germany; 2Department of Neuropathology, Munich, Germany; 3Department of Clinical Radiology, Munich, Germany; 4Department of Neurosurgery, Munich, Germany

The favorable prognostic impact of mutations in the IDH1 gene is well documented for malignant gliomas; its influence on WHO grade II astrocyto-

mas, however, is still under debate. A previously published database of 127 predominantly surgically treated patients harboring WHO grade II astrocyto-

mas was revisited. Patients were screened for TP53 mutations (sequencing analysis), IDH1 mutations (pyrosequencing), and MGMT promoter methylation (methyltion-specific polymerase chain reaction (MSP) and bisulfite sequencing). Endpoints were overall survival (OS), progression-free survival (PFS), time to progression (TTP), transformation into WHO grade III or IV disease (TR), and post-recurrence survival (PRS). Radiotherapy was usually withheld until tumor progression or malignan
t transformation occurred. IDH1 mutations, TP53 mutations, and methylated MGMT promoters were seen in 78.1%, 51.2%, and 80.0% of the analyzed tumors, respectively. IDH1 mutations, which were significantly associated with TP53 mutations and (or) MGMT promoter methylation (p < 0.001), resulted in shortened PFS (median 47 vs. 84 months; p = 0.004); PRS, however, was significantly increased in those patients undergoing malignant transformation (median: 49 vs. 13.5 months; p = 0.006). Overall survival was not affected by IDH1 mutation status. A new putative factor influencing malignant glioma with linkage into the EGFR signaling pathway expands our knowledge of TRIM11 biology and opens the door to exploring a potential new translational target for malignant glioma therapy. Highlights: 1) TRIM11 is up-regulated in high-grade glioma GSCs, but not in low-grade glioma GSCs and NSCs studied in appropriate in vitro conditions relative to their cell type. 2) The expression pattern of TRIM11 strongly correlates with that of CD133 and nestin in GSCs. 3) TRIM11 promotes the proliferation, migration, and invasion of malignant glioma cells. 4) TRIM11 modulates EGFR expression, possibly through regulating the transcription of HB-EGF

NO-75. BRAIN METASTASIS FROM NON-SMALL CELL CARCINOMA INITIALLY TREATED WITHOUT WHOLE BRAIN IRRADIATION: A RETROSPECTIVE ANALYSIS OF A CASE SERIES. Alejandro D. Muggers, Juan P. Alderuccio, and Blanca D. Diez; FLENI, BUENOS AIRES, Argentina

We sought to assess in patients with brain metastasis from NSCLC, survi-

val from diagnosis of brain metastases (OSbm), and median cerebral progression-free survival (PFSc) at 6 and 12 months. We also sought to deter-

mine whether KPS <70 or ≥70, multiple or single brain metastases, age <50 or ≥50 years, synchronous or metachronous metastases, and gender impact PFSc and OSbm. Finally, we sought to determine site of relapse

and cause of death. We analyzed 31 patients treated initially with surgery, radiotherapy, and/or focal radiotherapy with or without chemotherapy and without whole brain irradiation (WBI) from July 2007 to February 2011 with a minimum follow-up of 4 months. The median age was 58 years (36-77), and 14 patients were male. Median follow-up from diagnosis of brain metastases was 9 months (1-46). Ten patients had a solitary metas-

tasis. PFSc and OSbm were calculated by Kaplan-Meier, and log rank test

was used to test associations. Initial Treatment: 12 patients had surgery, 13 patients had surgery followed by radiosurgery, 8 patients had radiosurgery, and 1 patient had local radiation therapy. Seventeen patients (55%) had progression of CNS disease, of which 3 (9.6%) were only in the treated site, 4 (13%) in the initial site and distant within the CNS, and 12 (39%) only in a distant CNS site. Four patients underwent WBI at pro-

gression. Six-month PFSc and OSbm were 63% and 66%, respectively, and 12-month PFSc and OSbm were 27% and 53%, respectively. Median PFSc and OSbm were 8.6 months and 14 months. Statistically significant difference was found in OSbm in patients with KPS ≥70 (p = 0.014) com-
pared to patients with KPS <70. In 5 patients, the cause of death was neuro-

logic progression. The median OSbm was 14 months. Median PFSc was 8.6 months. The only statistically significant association was between OSbm and KPS ≥70.

NO-76. PERSONALIZING DRUG SCREENING FOR GLOBLASTOMA MULTIFORME (GBM) PATIENTS. Pengfei Jiang, Ying Chao, Matthew Gallagher, Ryan Kim, Sandra Pastorino, Valentina Fogal, and Santosh Kesari; Moores Cancer Center of UCSD, La Jolla, CA

After successfully culturing and expanding primary tumor cells from fresh brain tumor tissue samples, we screened the FDA-approved oncological drug set to find potent drugs for brain tumor patients. All positive drugs were already used in other kinds of cancer therapy, but not for brain tumors. For GBM patients, we personalized drugs based on the drug responses in vitro screening. Another consideration is pharmaceutical features of the positive drugs, such as capability to penetrate the blood-brain barrier (BBB). We also investigated the mechanisms of successful drugs for GBM patients. Designing personalized treatments for GBM patients based on these results may make more rational chemotherapeutic strategies possible.

NO-77. THE EARLY EXPERIENCE WITH DR. BEAT: A PHASE IIA STUDY OF THE ADDITION OF TEMOZOLOMIDE TO A STANDARD CONDITIONING REGIMEN FOR AUTOLGOUO STEM CELL TRANSPLANTATION IN RELAPSED AND REFRACTORY CENTRAL NERVOUS SYSTEM (CNS) LYMPHOMA. Jeremy D. Rudnick, Catherine Bresee, Andre Rogatko, Sonya Sakowsky, Mercedes Franco, Jethro Hu, Stephen Lim, Angela Lopez, Lilian Yu, Keri Ryback, Vivian Tsang, Michael Lill, and Amir Steinberg; Cedars Sinai Medical Center, Los Angeles, CA

This is a phase IIA, single institution trial to evaluate the safest dose of temozolomide that can be incorporated into a conditioning regimen (DRBEAT) for autologous hematopoietic stem cell transplant (ASCT) for relapsed or refractory primary CNS lymphoma (PCNSL) or DLBCL with brain involvement. ASCT is rapidly becoming the standard of care for relapsed CNS lymphoma after high-dose methotrexate. The melphalan used in BEAM, a standard transplantation regimen, is thought to have poor CNS penetration. Temozolomide, an alkylating agent known to penetrate the CNS and approved by the FDA for brain tumors, is used frequently for relapsed/resistant CNS lymphomas. The most effective dose for this disease is unknown and dose-limiting toxicity is primarily thought secondary to bone marrow suppression. We sought to
determine the maximum tolerated dose (MTD) using escalation with over-
dose controls (EWOC) as an adaptive dose-finding design. In our regimen, the D represents decadrion, a steroid which is used as a standard premedica-
tion in the RBEAM regimen. The main difference between the RBEAM regimen and the DRBEAT is the replacement of melphalan with temozolomide. Temozolomide is given as a daily dose either IV or PO over five days starting on day -5 of the ASCT. We are presenting the results of our first three patients dosed with an alpha .05 and theta .40 and treated

NO-78. PERSONALIZING DRUG SCREENING FOR GLOBLASTOMA MULTIFORME (GBM) PATIENTS. Pengfei Jiang, Ying Chao, Matthew Gallagher, Ryan Kim, Sandra Pastorino, Valentina Fogal, and Santosh Kesari; Moores Cancer Center of UCSD, La Jolla, CA

After successfully culturing and expanding primary tumor cells from fresh brain tumor tissue samples, we screened the FDA-approved oncological drug set to find potent drugs for brain tumor patients. All positive drugs were already used in other kinds of cancer therapy, but not for brain tumors. For GBM patients, we personalized drugs based on the drug responses in vitro screening. Another consideration is pharmaceutical features of the positive drugs, such as capability to penetrate the blood-brain barrier (BBB). We also investigated the mechanisms of successful drugs for GBM patients. Designing personalized treatments for GBM patients based on these results may make more rational chemotherapeutic strategies possible.
with escalating doses of 250, 287, and 351 mg/m² daily × 5 days. To date, we have had no unexpected dose-limiting toxicity or difficulty with enrollment. Because of swallowing difficulty, we had utilized the IV formulation in one case. This is the first time to date we believe anyone has used EWOC in an ASCT protocol, and we will discuss the challenges in optimizing this technique for which DLTs are expected.

NO-78. TREATMENT OUTCOMES FOR PATIENTS WITH ANAPLASTIC Astrocytomas TREATED WITH RADIATION AND TEMOZOLOMIDE (TMZ) AND MAINTENANCE TMZ
Raivi Sheth, Sean Grimm, Irene Helenowski, Alfred Rademaker, and Jeffrey Raizer; Northwestern University, Chicago, IL

BACKGROUND: Patients with anaplastic astrocytomas (AAs) are either treated at diagnosis with radiation therapy and chemotherapy or chemoradiation using TMZ followed by maintenance TMZ. The optimal treatment regimen for patients with AAs is not defined, but studies are underway to determine this. We did a retrospective review of our patients with AA treated with chemoradiation using TMZ followed by maintenance TMZ and assessed for PFS-6, TTP, and OS. METHODS: We reviewed our database for patients diagnosed with anaplastic glioma between 8/1/2000 and 12/31/2010 who were treated with TMZ followed by maintenance TMZ. Our inclusion criteria included age >18 yrs, newly diagnosed AA with no prior treatment, and sufficient data/follow-up. Those without sufficient data were excluded. Data were analyzed to determine PFS, TTP, and OS. RESULTS: 28 patients were identified (14 men and 14 women) with a median age of 45 yrs (24-76) and median KPS of 90 (70-100). All patients were treated with chemoradiation, and 2 received arsenic trioxide during RT and 1 received avastin during the maintenance phase of TMZ. Identifiable adverse events included: AA (n=23), OA (n=3), or anaplastic glioneuronal tumor (n=2). The extent of resection was: GTR 25%, STR 57%, and biopsy 18%. The Median number of cycles was 10.5 (0-24). The median TTP was 18.5 months, and PFS-6, -12, and -24 were 96.1%, 73.1%, and 51.6% respectively. Median OS was 34.4 months, 12, 24, and 60 months of 92%, 63%, and 53.2%, respectively.

CONCLUSIONS: There is currently no standard treatment for AAs. Data from NOA-04 indicate that initial treatment with chemotherapy or RT are the same, but long-term follow up in comparison to our study cannot be made, but our data is somewhat similar. Ongoing trials should help identify a standard AA treatment.

NO-79. MENINGIOMA RESPONSE TO BEVACIZUMAB: A RETROSPECTIVE ANALYSIS OF TREATMENT RESULTS IN 14 NF2 PATIENTS
Fabio P. Nunes, Vanessa Merker, Dominique Jennings, Paul Caruso, Álona Mizukinszky, Anat Stemmer-Rachamimov, and Scott Plotkin; Massachusetts General Hospital, Boston, MA

INTRODUCTION: Meningiomas are a major cause of morbidity and mortality in patients with neurofibromatosis 2 (NF2). No medical treatments are currently available for tumors that are not amenable to surgical resection or radiation therapy. Recently, we have demonstrated that bevacizumab, an anti-VEGF antibody, improves hearing function and decreases vestibular schwannoma (VS) size in some NF2 patients. METHODS: To determine the response of meningiomas to bevacizumab, we performed a retrospective analysis of 14 NF2 patients with meningiomas who were treated with bevacizumab for progressive VS between 2007 and 2010. Patients received bevacizumab 5 mg/kg i.v. every two weeks. Baseline MRI scans were performed approximately 1 month prior to the start of treatment, and followup MRI scans were performed every 3-6 months after therapy was initiated. A radiographic response was defined as ≥20% decrease in tumor volume compared with baseline measurements; progression was defined as ≥20% increase in volume from baseline measurements. All other responses were considered stable disease (SD). RESULTS: Six meningiomas were treated with bevacizumab for a median of 15.5 months (range 6-36 months). The mean patient age was 29.5 years (range 16 to 63 years). A total of 40 meningiomas (mean 2.85/patient) were analyzed for response to therapy. A radiographic response was defined as 54% (40 tumors responded to therapy and others progressed in the same post-treatment period). Over the duration of the study, only seven tumors (17.5%) remained responsive, whereas 20 progressed (50%) and 13 remained stable (32.5%). There was no correlation between tumor response in a single patient; some meningiomas responded to therapy and others progressed in the same patient. CONCLUSION: Our results suggest that bevacizumab was effective in decreasing meningioma size in a minority of patients. A phase 2 study of bevacizumab in NF2 patients is ongoing and will help clarify the effect of bevacizumab treatment in this population.

NO-80. CONCURRENT BEVACIZUMAB (BEV), TEMOZOLOMIDE (TMZ), AND IRRADIATION (RT) IMPROVES SURVIVAL IN Glioblastoma PATIENTS COMPARED TO CONCURRENT RT and TMZ RESERVING BEV and TMZ FOR SALVAGE THERAPY
Aaron C. Spalding, Todd W. Vitzt, David A. Sun, and Sarah Parsons; Brain Tumor Center, Louisville, KY

PURPOSE/OBJECTIVES: Bevacizumab (BEV) is FDA-approved for treating the progression or recurrence of glioblastoma (GBM). We tested the hypothesis that integration of BEV into standard radiation (RT) with temozolomide (TMZ) improves progression-free survival (PFS) and overall survival (OS) compared to RT + TMZ alone.

MATERIALS/METHODS: Under an IRB-approved protocol, we reviewed the treatment of 32 patients with GBM who received RT delivered either with concurrent and adjuvant BEV and TMZ (combined, n = 23) or TMZ alone (standard, n = 9). MRI scan with gadolinium was done before initiation of adjuvant therapy and every 3 months afterward. Patients received adjuvant therapy until either progression or 12 months after completion of RT. Progression was defined based on MRI changes, a change in therapy, death, or new clinical symptoms. All patients who progressed on standard therapy received BEV as salvage therapy.

RESULTS: There was no significant difference between the combined and standard cohorts with respect to age, extent of resection, performance status, or radiation dose (P > 0.05). With a median follow up of 16 months improved PFS (72%) versus the standard arm with BEV as salvage (37%). CONCLUSION: Our results with standard RT + TMZ therapy are similar those reported by the EORTC/NCIC in terms of PFS and OS. The addition of BEV concurrently with RT + TMZ and as an adjuvant to TMZ improves PFS and OS. Reserving BEV for salvage therapy at the time of progression does not produce equal survival compared to concurrent administration.

NO-81. OUTCOME OF THE OLDEST OLD WITH PRIMARY CENTRAL LYMPHOID TUMORS: MEMORIAL SLOAN-KETTERING CANCER CENTER (MSKCC)
Mary R. Welch, Antonio Oimmel, and Lisa M. DeAngelis; Memorial Sloan-Kettering Cancer Center, New York, NY

INTRODUCTION: Up to 20% of patients diagnosed with PCNSL are aged ≥80, yet optimal treatment for this growing demographic remains poorly defined. METHODS: This was a retrospective review of PCNSL patients diagnosed at age ≥80 and treated at MSKCC since 1993. Toxicity was analyzed by chart review, and response was determined by contrast-enhanced MRI. RESULTS: Sixteen patients (age 80-90) were identified with a median age of 81.5. Nine (56%) were women, and the median KPS at diagnosis was 80. Fifteen patients (94%) received a median of 5 cycles of a methotrexate-based regimen. Baseline creatinine clearance ranged from 28-73 ml/min (median, 55). Twelve patients (75%) were treated with 3.5 g/m² of MTX; reduced doses (1-3 g/m²) were used in the remaining three patients. One patient underwent upfront WBRT; a second received ocular RT and a third, spinal RT. Complete response was achieved in 7/16 patients (44%). Fifteen patients (94%) maintained or improved their baseline KPS over the course of treatment, and among responders, the median KPS after treatment was 90 (60-90). Ten patients (63%) returned home, 5 with MTX; one died of sepsis after his third cycle had cleared; and five (31%) were discharged to either hospice or nursing home. One year survival rate from time of diagnosis was 25%; two year survival was 19% and three year survival 12.5%. Overall, chemotherapy was well tolerated. The most commonly observed MTX-related toxicity was renal insufficiency requiring cessation of treatment after 4 of 5 planned cycles. CONCLUSIONS: High-dose methotrexate is feasible among select PCNSL patients aged ≥80 and may result in durable responses and improved KPs.
BACKGROUND: The addition of bevacizumab allows for more aggressive RT schedules such as HFSRT. In 60 patients with tumor volumes less than 60cc were eligible. HFSRT was given in 6 treatments over 2 weeks: 6x6 Gy to the contrast-enhancing tumor and 6x4 Gy to the FLAIR hyperintensity with dose painting conventional with bevacizumab (10 mg/kg Q2 weeks) and temozolomide (75mg/m2 daily) and followed by adjuvant bevacizumab/temozolomide (150-200 mg/m2 in 5/28 days). Followup included perfusion MRI (PWI) and neuropathological assessment (NPA). Primary endpoint was 1-year OS (SO); secondary endpoints were OS (18 months), PFS, and Grade 3-4 nonhematologic toxicities included pulmonary embolism (2), renal failure (1), wound infection (1), and colitis (1); one patient died on study from an unknown cause. The median progression-free survival (PFS) was 11 months (95%CI 9-15). No patient had pseudoprogression. Among 30 evaluable patients, response (Macdonald criteria) was complete in 11 (37%), partial in 14 (47%), stable in 5 (17%), and progressive in 0 (0%). Median OS was 11 months (95%CI 9-15). No patient had pseudoprogression.

METHODS: FET-PET studies were performed on 18 glioma patients with H63D mutation was shorter than that of male GBM patients with wild type IDH

results, and no AE led to the discontinuation of everolimus. This study confirmed that long-term treatment with everolimus is safe and effective for patients with SEGAs associated with TSC; SEGAs volume reductions have been maintained in patients receiving everolimus for up to 3 years. Patients with TSC develop a variety of benign tubers in multiple organ systems. In the CNS, manifestations include SEGA, cortical tubers, epilepsy, and neurocognitive and behavioral problems. Long-term survival of GBM patients 

NO-83. HFE GENOTYPE PREDICTS PATIENT SURVIVAL IN GLOBLASTOMA MULTIFORME INDEPENDENT OF IDH1 GENOTYPE

Sang Y. Lee, Becky Slagle-Webb, Michael J. Glantz, Jonas M. Sheehan, and James R. Connor; Penn State College of Medicine, M.S. Hershey Medical Center, Hershey, Pennsylvania

The HFE protein plays a key role in the regulation of cellular iron uptake. Cancer cells have a robust iron appetite, and therefore, it is logical that mutations in proteins that regulate cellular iron could impact cancer cell phenotype. HFE polymorphisms are common genetic variants in Caucasians. Mutations at amino acid site 63 (H63D) and 282 (C282Y) are the two most common HFE gene variants and result in increased iron accumulation in cells. We have previously reported that human astrocytoma and neuroblastoma cell lines are resistant to temodar and radiation. Therefore, we predicted that HFE polymorphisms would impact survival in patients with glioblastoma multiforme (GBM). The length of survival was defined as the time from the date of diagnosis to the date of the last contact or death in GBM patients (n = 56) was significantly different between wild-type (WT) patients and H63D carriers. All H63D-carrying GBM patients died within a year of diagnosis. In addition, the median survival of male GBM patients with H63D mutation was shorter than that of male GBM patients with wild type HFE. NAD(P)+/H-dehydrogenase 1 (IDH1) genotype is also reportedly correlated with survival of GBM patients. We are in the process of evaluating our GBM patients for IDH1 genotype and to date 29 have the wild type form of IDH1; the impact of HFE polymorphism status appears independent of IDH1. These data indicate that H63D HFE polymorphism is associated with poor GBM patient survival.

NO-84. INFLUENCE OF FLUOROETHYL TYROSINE-PERSON-TRONOMIMETRY (FET-PET) IN THE DAILY ROUTINE DECISIONMAKING PROCESS OF THE THERAPY OF RECURRENT MALIGNANT GLIOMA

Claudia A. Schlimper1, Holger Schlag1, Gabriele Stoffels2, and James R. Connor1; 1Hospital of Cologne, Cologne, Germany; 2University of Cologne, Cologne, Germany

INTRODUCTION: Imaging techniques are important for accurate diagnosis and follow-up. 11C-labeled MNI is the gold standard. However, this technique reflects biological activity of the tumor. Fluoroethyltyrosine (FET) is an amino acid marker with high specificity for tumor metabolism. We evaluated the influence of FET-PET for detecting the recurrence of WHO-grade II and a malignant WHO-Grade III gliomas.

METHODS: FET-PET studies were performed on 18 glioma patients (8 patients with glioblastoma multiforme WHO Grade IV and 10 patients with glioma WHO grade III). All patients underwent magnetic resonance imaging (MRI) and 18F-FDG PET/CT. Initial staging was performed by the Research Center Jülich. We assessed the tumor’s maximal area and the tumor recurrence area. CONCLUSION: Additional metabolic information was provided by FET-PET. In our study, FET-PET had a significant influence on the decision to perform an operation or biopsy in patients with suspicion of tumor recurrence and size of tumor recurrence. In these cases PET gave us detailed information about the extent of tumor tissue and potential for malignant transformation.

NO-85. LONG-TERM SAFETY AND EFFICACY RESULTS OF ORAL EVEROLIMUS IN PATIENTS WITH SUBEPENDYMAL GIANT CELL ASTROCYTOMAS (SEGA) IN TUBEROUS SCLEROSIS COMPLEX (TSC)

Darcy A. Krueger1, Margot A. Care1, Katherine Holland1, Karen Agricola2, Cynthia Tudor2, Anna Byars3, Tarek Sahnoud4, and David N. Franz1; 1Cincinnati Children’s Hospital Medical Center, Cincinnati, OH; 2Novartis Pharmaceuticals Corporation, Florham Park, NJ

In patients with TSC develop a variety of benign tubers in multiple organ systems. In the CNS, manifestations include SEGA, cortical tubers, epilepsy, and neurocognitive and behavioral problems. In a phase 1/2 study in patients with SEGAs associated with TSC, the mammalian target of rapamycin (mTOR) inhibitor everolimus significantly reduced SEGA volume within a few months without the need for surgical intervention (Krueger et al. NEJM 2010;363:1801-1811). Seizure frequency also decreased. The study was an open-label extension phase to determine the long-term safety and efficacy of oral everolimus (triatated to achieve a target trough concentration of 5-15 ng/mL) in treatment of these patients. Of 28 patients enrolled in the initial study, 25 were still receiving everolimus at the extension study cut-off date (31-Dec-2010). Median treatment duration was 1041 days (range, 142-1434), and the median dose was 5.29 mg/m2/day (range, 2.1-12.3). Reduction of the primary SEGA volume by ≥30% from baseline occurred in 79.2%, 64.7%, and 77.8% of patients at 24, 30, and 36 months, respectively, and reduction of SEGAs by ≥ 50% from baseline in 50.4%, 41.2%, and 55.6% of patients at 24, 30, and 36 months. The ≥30% reduction in primary SEGAs was maintained for a median of 25.8 months (up to progression or the cut-off date). Adverse events (AEs) were mostly grade 1/2 in severity and were consistent with those previously reported. Over the follow-up duration of the extension study, 5 cases of grade 4 profusion of SEGAS, 2 cases of encephalopathy, 4 cases of grade 3 dermatitis, sinusitis, viral bronchitis, and concomitant neutropenia were reported at <12 months, 23-36 months (stomatitis, pneumonia, and limb abscess), and 36-38 months (neutropenia). No drug-related grade 4 events were reported, and no AE led to the discontinuation of everolimus. This study confirmed that long-term treatment with everolimus is safe and effective for patients with SEGAs associated with TSC; SEGAs volume reductions have been maintained in patients receiving everolimus for up to 3 years.

NO-86. A PHASE I TRIAL OF LAROMUSTINE (VPN40101M) AND TEMOZOLOMIDE FOR PATIENTS WITH MALIGNANT GLIOMAS IN FIRST RELAPSE OR PROGRESSION

Jeffrey Kaper1, Laurie Rice, Alfred Rademaker, James Chandler, Robert Levy1, Kenji Murao, and Sean Grimm; Northwestern University, Chicago, Illinois

BACKGROUND: Effective treatments for recurrent malignant gliomas are limited. MGMT is one of the mechanisms of resistance for malignant gliomas. Deletion of MGMT may improve anti-tumor activity by increasing the activity of alkylators. We used this concept to perform a phase I trial of temozolomide (TMZ) and chloroethamine. METHODS: Patients were enrolled in a single-site, open-label 3 + 3 phase I trial at the MTD. Patients were treated with TMZ at 75 mg/m2 on days 1-7 and then chloroethamine at 100, 150, or 125mg/m2 on day 7 (2 hours after TMZ) for a 6 week cycle. Patients were treated until progression or intolerable side effects. Patients had brain MRI every 6 weeks with a physical exam and weekly CBC. RESULTS: A total of 14 patients were enrolled (10 GBM, 3
radiographic recurrence, and he was treated with temozolomide (200 mg/m²). He tolerated the therapy well, but he had recurrence of partial seizures. MRI after the third cycle of temozolomide showed tumor progression. The patient was started on bevacizumab monotherapy (10 mg/kg every 2 weeks). He tolerated the treatment well but had blood pressure elevation, which was effectively treated with amiodipine. After two cycles, the seizures were controlled, and MRI revealed an almost complete resolution of the enhancing lesion (partial response by RANO criteria [8]). Bevacizumab appears to be a tolerable and effective treatment for recurrent progressive ganglioglioma.

NO-88. BEVACIZUMAB FOR TREATMENT OF RECURRENT GANGLIOGLIOMA
Alissa A. Thomas, Camilo E. Fadul, Louise P. Meyer, and Enrico C. Lallana; Dartmouth Hitchcock Medical Center, Lebanon, NH

Gangliogliomas are tumors that have glial and neuronal components and are known to have benign histology with a favorable prognosis (1). Treatment is surgical, and gross-total resection is curative (1,2). Radiation therapy is reserved for recurrences or malignant transformation. There is little evidence for chemotherapy, but there are case reports of successful treatment of congenital malignant gangliogliomas and pediatric low grade progressive gangliogliomas with carboplatin alone or in combination with etoposide (3,4,5). We describe a case of a 23-year-old man with recurrent left temporal lobe ganglioglioma treated with bevacizumab. Bevacizumab is a humanized monoclonal antibody that inhibits the activity of vascular endothelial growth factor (VEGF), a fact that provides the rationale for exploring treatments such as the anti-VEGF monoclonal antibody bevacizumab. METHODS: We retrospectively reviewed the records of nine patients with WHO grade II and III multiply recurrent meningiomas who received antiangiogenic therapy with bevacizumab. We focused on progression free survival, overall survival, radiographic response, and toxicity. RESULTS: Nine patients (4 men, 5 women) with a median age of 52 years (range, 34-81) received treatment with bevacizumab for Grade II or III meningioma. Four patients had pathological diagnosis of atypical (Grade II) meningioma, and 5 had anaplastic (Grade III) meningioma. All patients had received prior surgery and radiation and were not candidates for either. Bevacizumab was administered at 10mg/kg every 2 weeks for a median of 7 treatments (range, 1-16). The best radiographic response was a minor size reduction in three (≥30% reduction in tumor) and stable disease in five patients; scan is pending in 1 patient. At a median follow-up of 7 months (range 2-22), 2 patients progressed and died. Seven patients are alive, 2 of whom developed intratumor hemorrhage; bevacizumab was discontinued in these 2 patients. CONCLUSION: Antiangiogenic therapy may be an effective strategy for treatment of recurrent meningiomas that are ineligible for further surgery and radiotherapy. Two patients developed nonfatal intratumoral hemorrhage after receiving bevacizumab. Further studies are needed to determine the safety and efficacy of bevacizumab in this setting.

NO-89. A PHASE I STUDY OF SORAFENIB WITH RADIATION AND TEMOZOLOMIDE IN NEWLY DIAGNOSED Glioblastoma
Howard Colman1, Mark Gilbert2, W.K. Alfred Yung3, Ken Aldape3, John De Groot4, Charles Conrad3, Victor Levin2, Morris Groves3, Monica Loghin4, Pelloski Chris3, and Vinay Puduvalli4; Huntsman Cancer Institute, University of Utah, Salt Lake City, UT; 3UT MD Anderson Cancer Center, Houston, TX; 4Ohio State University, Columbus, OH

Increased angiogenesis and activation of the MAP kinase pathway are associated with poor prognosis in glioblastoma (GBM). Sorafenib is a multi-targeted small molecule inhibitor that targets both the Raf/MAPK kinase pathway and VEGF receptors and is thus a potentially attractive agent for overcoming resistance to standard therapy. We conducted a Phase I study to determine the maximum tolerated dose (MTD) and toxicity profile of sorafenib given both concurrently with chemoradiation and in the adjuvant setting along with standard dose temozolomide. Dose Level 1 consisted of sorafenib (400mg BID) given after radiation therapy along with standard dose adjuvant temozolomide. A total of 10 patients were enrolled, of which 6 were evaluable. One DLT was observed (grade 3 wound dehiscence), although dose reductions were needed in subsequent cycles in approximately 50% of patients. Dose Level 2 consisted of sorafenib (200mg BID) given during radiation therapy on concurrent temozolomide and followed by sorafenib (400mg BID) given after radiation therapy with temozolomide. At this dose level, a total of 8 patients were enrolled, of which 6 were evaluable. A total of 3 DLTs were observed, including grade 4 rash and hematoma and grade 4 decreased hemoglobin, which indicated a breach of the MTD. In terms of patient outcomes, two patients at Dose Level 1 completed 12 cycles of adjuvant temozolomide and sorafenib without progression, whereas two other patients progressed during the initial 12 months. The remaining patients are continuing treatment without evidence of progression. Although the progression-free survival outcomes observed to date are promising and will be updated as time proceeds, we conclude based on current results that the combination of sorafenib with standard chemoradiation and adjuvant temozolomide is associated with significant toxicities (particularly during the chemoradiation portion) without a striking clinical benefit, and the decision was made not to pursue a Phase II study at this time.

NO-90. THE DIMINISHING IMPACT OF AGE AS A PROGNOSTIC FACTOR FOR Glioblastoma PATIENTS IN THE ERA OF BEvacizumab
Seema Nagpal, Abdullah Feroze, and Lawrence Recht; Stanford University, Stanford, CA

Multiple studies identify old age as a negative prognostic factor in glioblastoma. As a result, practicing physicians may be nihilistic in their approach to treating elderly patients, and clinical trials routinely restrict enrollment after age 70. We have noted that the impact of age seems less powerful since the introduction of bevacizumab (BEV) and conducted a retrospective analysis of 185 glioblastoma patients ranging from 22 to 93 years old to assess this impression. All patients were treated at our center from 2004 to 2010. 75% of these patients received BEV. In the total cohort, overall survival was longer in patients who received BEV (20.8 ± 10.1 months, p < 0.001 log rank). This survival benefit was also significant in patients > 70 receiving BEV (12.4 ± 4.7 months, p < 0.001 log rank). The group that did not receive BEV, the difference in survival between patients stratified according to age groups <50, 50-69, and >70 was statistically significant (medians 13.5, 15.1, and 4.0 months, respectively; <0.001, log rank). In patients who received BEV, there was no significant difference between the age groups (22.3, 21.1, and 12.4 months, p = 0.24 NS, log rank). Based on these data, we conclude that the introduction of BEV has diminished the impact of age on outcome and suggest that the practice of excluding patients from trials solely on the basis of age should be reconsidered.
NO-91. RECURRENT PAPILLARY TUMOR OF THE PINEAL REGION (PTPR) IN A PEDIATRIC PATIENT: A BRIEF REPORT
Hemalatha G. Rangarajan1, Mark W. Kircher2, Robert M. Scott2, Sean M. Lew1, Noura Y. Faraq1, James D. Segar1, and Sachadewa1;
1Medical College of Wisconsin, Milwaukee, WI; 2Dana-Farber Cancer Institute, Boston, MA.

Papillary tumors of the pineal region are rare tumors arising from the specialized ependyma of the subcommissural region and represent <1% of all intracranial tumors. Immunohistochemistry helps to differentiate these from closely related choroid plexus tumors and papillary ependymoma.

We report a child with a recurrent papillary tumor of the pineal region. The patient presented at 11 years of age with a one-month history of nausea, vomiting, headache, and vision changes. MRI revealed a 2.1 cm mass in the pineal region with obstructive hydrocephalus. The tumor was immunoreactive for cytokeratin and vimentin, which is consistent with a diagnosis of papillary tumor of the pineal region.

NO-92. PETREXTED FOR PATIENTS WITH CENTRAL NERVOUS SYSTEM (CNS) METASTASES
Patricia U. Kumin1, Sean A. Grimm, Matthew Avram, J. Patel, V. Kaklamani, Katie McCarthy, Mary Cianfrocca, William Gradishar, Evanston Hospital Kellogg Cancer Center, Evanston, IL; 2University of California, Los Angeles, CA; 3MASSACHUSETTS GENERAL HOSPITAL, BOSTON, MA.

BACKGROUND: Treatment options for patients with CNS solid tumor metastases after WBRT are limited. Pemetrexed is a multitargeted antifolate agent approved for NSCLC with activity seen in several solid tumors.

METHODS: IRB approved consent was obtained in patients with solid tumor CNS metastases. These patients were in one of two trials and given one of four dose levels of pemetrexed: 500 (n=5), 750 (n=3), 900 (n=1), or 1000 mg/m² (n=3) every 3 weeks (cycle 1 through 6).

RESULTS: Twenty-one patients (15 women, 6 men) with a median age of 50 (range 26-70) and median KPS 90 (range 60-100) were treated. Primary tumor sites included breast (13), lung (4), colon (1), endometrial (1), cervical (1), and pinealoblastoma (1). Patients received pretreatment folic acid and B12 injections and continued on treatment until disease progression or the treatment could no longer be tolerated. RESULTS: Twenty-one patients (15 women, 6 men) with a median age of 50 (range 26-70) and median KPS 90 (range 60-100) were treated. Primary tumor sites included breast (13), lung (4), colon (1), endometrial (1), cervical (1), and pinealoblastoma (1). Patients received pretreatment folic acid and B12 injections and continued on treatment until disease progression or the treatment could no longer be tolerated. RESULTS: Twenty-one patients (15 women, 6 men) with a median age of 50 (range 26-70) and median KPS 90 (range 60-100) were treated. Primary tumor sites included breast (13), lung (4), colon (1), endometrial (1), cervical (1), and pinealoblastoma (1). Patients received pretreatment folic acid and B12 injections and continued on treatment until disease progression or the treatment could no longer be tolerated.

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CONCLUSION: Pemetrexed is tolerated in patients with solid tumor CNS metastases. Although the population studied was small, antitumor activity and chemotherapy needs to be addressed for these rare tumors.

NO-93. NCCTG PHASE II TRIAL OF BEVACIZUMAB IN COMBINATION WITH SORAFENIB (BEV/SOR) IN RECURRENT GLIOBLASTOMA (rGBM)
Evantha Galanis1, S Keith Anderson1, Jacqueline M. Lafky1, Timothy M. Mulcahy, J. Von Roenn, I. Helenowski, A. Rademaker, and J. Raizer; Northwestern University, Chicago, IL.

BACKGROUND: Bevacizumab is a targeted agent that blocks tumor angiogenesis through inhibition of the VEGF ligand-receptor interaction. Here we show that bevacizumab can be an effective treatment approach for surgically unresectable cervical cord hemangioblastoma. A 52 year old patient with surgically unresectable cervical cord hemangioblastoma and progressive quadraparesis was successfully treated with bevacizumab. After 6 cycles of bevacizumab, his tumor decreased in size from 2.7 x 1.0 x 1.5 cm to 2.0 x 0.8 x 1.5 cm as determined by MRI with contrast. To the best of our knowledge, this has never been reported in the past.

CONCLUSION: Pemetrexed is tolerated in patients with solid tumor CNS metastases. Although the population studied was small, antitumor activity is observed in 50% of patients (primarily breast) with most achieving disease stabilization.

NO-94. BEVACIZUMAB FOR THE TREATMENT OF SURGICALLY UNRESECTABLE CERVICAL CORD HEMANGIOBLASTOMA
Ayman1, Oman; Southern Illinois University School of Medicine, Springfield, IL.

Hemangioblastomas of the central nervous system commonly arise in the cerebellum and les commonly in the spinal cord. They express high levels of vascular endothelial growth factor (VEGF) and are therefore highly vascular tumors. Bevacizumab is a target inhibitor of VEGF through inhibition of the VEGF ligand-receptor interaction. We sought to describe actual treatment over 3 decades and explore the impact of VEGF-targeted therapy on outcomes.

NO-95. TIME TRENDS IN TREATMENT OF ANAPLASTIC OLIGODENDROGLIOMA TUMORS
Katherine S. Panagies1, Fabio M. Iwamoto1, Timothy F. Cloughesy1, Kenneth D. Aldape1, Andreae L. Rivera1, April F. Echleicht2, David N. Louis1, Nina A. Paleologou1, Barbara J. Fishert2, Lynn S. Ashby1,1, J.G. Caimiross2, Gloria B. Roldan3, Patrick Y. Wenz3, Keith L. Lignon3, David Schiffo1, H.L. Robins1, Brandon G. Rocque2, Marc C. Chamberlamin1, Warren P. Mason1, Susan A. Weaver1, Richard M. Green1, Francois G. Kamar2, Lauren E. Abrey1, Lisa M. DeAngelis1, Suresh C. Jhanwar1, Marc K. Rosenblum1, and Andrew B. Lassman1; 1Memorial Sloan-Kettering Cancer Center, New York, NY; 2University of California, Los Angeles, CA; 3MD Anderson Cancer Center, Houston, TX; 4Massachusetts General Hospital, Boston, MA; 5NorthShore University HealthSystem, Evanston Hospital Kellogg Cancer Center, Evanston, IL; 6London Regional Cancer Program, London, ON, Canada; 7Barrow Neurological Institute, Phoenix, AZ; 8University of California, Calgary, AB, Canada; 9Brigham and Women’s Hospital and Dana Farber Cancer Institute, Boston, MA; 10University of Virginia Health System, Charlottesville, VA; 11University of Wisconsin, Madison, WI; 12University of Washington and Seattle Cancer Care Alliance, Seattle, WA; 13Princess Margaret Hospital, Toronto, ON, Canada; 14Albany Medical Center, Albany, NY; 15Kaiser Permanente Angeles Medical Center, Los Angeles, CA; 16Clemenceau Medical Center, Beirut, Lebanon

INTRODUCTION: Treatment recommendations for newly diagnosed anaplastic oligodendroglioma (AO) or oligoastrocytoma (AOA) vary widely. We sought to describe actual treatment over 3 decades and explore clinical correlates of administered therapies.

METHODS: We previously conducted an international retrospective study of adults diagnosed 1984-2007 who were not enrolled in phase III trials for newly diagnosed
NO-97. NATURAL HISTORY AND CHARACTERISTICS OF BRAINSTEM AND CEREBELLAR GLIOMAS IN ADULTS

Brett F. Theeler,1 Isaac Melguizo-Gavilanes,1 Nicole A. Shonka,2 Xuemei Wang1, Anita Mahajan1, and Vinay Puduvalli1; 1MD Anderson Cancer Center, Houston, TX; 2Nebraska Medical Center, Omaha, NE

INTRODUCTION: Brainstem and cerebellar gliomas account for <5% of GBM. The purpose of this study is to describe the natural history and clinical features of brainstem and cerebellar gliomas in adults.

METHODS: We retrospectively reviewed records of adults with brainstem or cerebellar gliomas identified in the MD Anderson Cancer Center database from 1990-2010. RESULTS: We identified 153 patients with brainstem, and 82 with cerebellar glioma.

RESULTS: Median age at diagnosis was 55 years, and 90% were of glioblastoma multiforme. Of the brainstem tumors, the majority were located in the pons (55%) followed by medulla (39%) and midbrain (12%) in a diffuse (61%) or focal/exophytic (37%) manner. 28% were not biopsied; in the remainder, anaplastic glioma (AG; 26%), glial tumor grade unspecified (15%), glioblastoma (13%), and juvenile pilocytic astrocytoma (JPA; 10%) were most common histologies. Tumors were predominantly hemispheric (54%) or vermicular (39%) with the most common histologies being glioblastoma (39%), JPA (23%), and AG (20%). Oligodendrogliomas were rare and accounted for less than 2% of all brainstem and cerebellar gliomas. Patients with cerebellar gliomas had a better median overall survival (46.3 months) compared to those with brainstem gliomas (34.5 months; p = 0.06). Patients with JPA had the best prognosis regardless of location. Of brainstem tumors, focal/exophytic tumors had a significantly better median survival (51.3 months) than diffuse tumors (20.9 months; p = 0.01). Additionally, survival was poorest for patients with glioblastoma (12.1 months) and best for those with grade unspecified (90.3 months). Among cerebellar gliomas, patients with AG had better median survival (19.7 months) than those with glioblastoma (13.6 months). CONCLUSIONS: In this large series, we describe the natural history and histology of brainstem and cerebellar gliomas in adults and the relevance to outcome. Survival was similar for brainstem and cerebellar high-grade gliomas. Adults with diffuse brainstem gliomas have better survival than pediatric patients.

NO-98. ELEVATED GLUCOSE LEVELS AND SURVIVAL IN ELDERLY PATIENTS WITH NEWLY DIAGNOSED Glioblastoma

Neda Hashemi-Sadraei, Harpreet Bawa, Ganzeran Rahmatulla, Mital Patel, Paul Elson, Glen Stevens, David Peerheoom, Michael Vogelbaum, Robert Weil, Gene Barnett, and Manmeet S. Ahluwalia; Cleveland Clinic Foundation, Cleveland, OH

INTRODUCTION: Hyperglycemia has been associated with poor outcomes in many disease states including cancer. Hyperglycemia augments in vitro astrocytoma cell growth. We undertook this study to evaluate the relationship between preoperative glucose levels and survival in elderly patients with newly diagnosed glioblastoma (GBM).

METHODS: With IRB approval, the Cleveland Clinic Brain Tumor and Neuro-Oncology Center’s database was used to identify patients ≥65 years old at diagnosis with histologically confirmed GBM. Patients with known diabetes and those in whom preoperative glucose was not available within 30 days prior to surgery were excluded from the analysis. The analysis was based on a recursive partitioning algorithm that included preoperative glucose, Karnofsky performance scale score (KPS), and patient age because these are co-occurring prognostic factors.

RESULTS: 242 GBM patients were a
median age of 74 (range 65-91, 52% male) were included. 32% of patients underwent gross total resection, 6% had near total resection, 19% had subtotal resection, and 43% had biopsy only. Following surgery, 74% of patients underwent radiation, and 43% received chemotherapy. Median preoperative glucose was 123 mg/dL (range 69-306). Median overall survival was 5.2 months (95% CI, 4.7-6.6 months). Patients were divided into 4 groups: group one (KPS > 70, age < 75 and preoperative glucose < 100 mg/dL), group two (KPS > 70, age > 75, and preoperative glucose > 100 mg/dL), group three (KPS > 70, age > 75, any glucose level), and group four (KPS < 70, any age, any glucose level). Median survival times for patients in groups one, two, three, and four were 14.0, 7.9, 5.1, and 3.0 months, respectively. Compared with patients in the favorable group (groups one and two), those in groups three and four were at progressively higher risk of dying (P < 0.001). CONCLUSION: Higher preoperative glucose level is associated with decreased overall survival in elderly GBM patients. Strict glucose control may contribute to improved outcome in treatment of these patients.

NO-100. KNOW THY ENEMY: PARADOXES TO BE EXPLOITED IN GliOBLASTOMA
Ellsworth C. Alvord1, Russell C. Rockne1, Jason K. Rockhill1, Maciej M. Drgalia1, Mark L. Spence1, Alan Rosomsky1, Alibert Li1, Timothy G. Goodenow1, Joanna Wardlaw1, Alexander M. Spence1, and Kristin R. Swanson1
1University of Washington, Seattle, WA; 2University of California Los Angeles, Los Angeles, CA; 3University of Dundee, Dundee, Scotland, United Kingdom

In the past 50 years, virtually no progress has been made in understanding the biology and treatment of glioblastoma, and the median prognosis has not changed significantly. For the first time, we may have a useful tool in the war against glioblastoma. We have observed paradoxes in tumor growth and response to therapy that we believe can be exploited and used against the tumor enemy. Using a patient-specific mathematical model for glioblastoma growth and invasion, we have calculated the growth rates of 35 glioblastomas and revealed that although about two-thirds of the patients have survived relatively long times, only about half of these can be attributed to their treatments. In other words, the other half of the long-surviving patients have not survived longer than would be predicted from their rates of growth if not treated. This contradiction is due to two paradoxes in their responses to treatment: 1) patients with some of the most rapidly growing glioblastomas benefit the most but still survive only slightly longer than the average, and 2) patients with some of the most slowly growing glioblastomas benefit the least but still survive longer than the average. These interpretations are possible only because the growth rates have been measured in the 35 patients and are impossible to reach in other population has not survived longer than would be predicted from the literature. RESULTS: Twenty patients had SCAs. Four were treated recently and had a very short followup. Sixteen patients were needed to detect an absolute improvement of 14% to 25% over a historical baseline of 11%. RESULTS: Interim analysis of stage 1 (n = 29) suggested efficacy. Because treatment-related toxicity was infrequent at 100 mg bid, stage IIb allowed escalation by 50 mg daily every cycle as tolerated (maximum 200 mg bid). Escalation was tolerable in 10/17 patients, but there were no responses, and 6mPFS was achieved in only in 2/31 (6%) patients. Among eligible patients (stages 1 and 1B, n = 52), the median PFS was 1.7 months, OS 7.5 months, and 6mPFS rate < 10% with no responses. The clinical benefit rate was too low to correlate tumor phenotype with activity. The trial was closed without proceeding to stage 2. CONCLUSION: Dasatinib as monotherapy is not effective in recurrent GBM, despite higher doses. Intrapatient dose escalation of dasatinib was feasible in most patients; therefore, future trials of dasatinib in combination regimens for GBM may be able to use higher doses than the usual monotherapy dose.

NO-101. SILENT CORTIOTROPH ADENOMAS, A COMPARISON WITH NON-FUNCTIONAL ADENOMAS
Gelareh Zadeh, Husseim Alahmadi, Jefferson Wilson, and Fred Gentili
University of Toronto, Toronto, ON, Canada

BACKGROUND: Silent corticotroph adenomas (SCAs) represent a distinct pathological entity of non-functional adenomas (NFAs) with some clinical features suggesting a distinct clinical behavior and recurrence potential. METHODS: We conducted a retrospective review of all SCAs at our institution over the last 10 years. Clinical, radiological, and pathological features were reviewed. The series was compared to a matched cohort of NFAs. Statistical analysis was carried out to detect statistically significant trends. Results were compared to the literature. RESULTS: Twenty patients had SCAs. Four were treated recently and had a very short followup. Sixteen patients were included in the final analysis. Nine patients (56%) were female. Mean age was 52 years (range 24-78 years). Six patients (38%) had visual compromise on presentation. Two patients (12.5%) presented with apoplexy. Two patients presented with secondary amenorrhea (1 silent corticotroph and 1 somatotroph adenoma). Two patients presented with apoplexy. Two patients presented with headache and 1 patient presented with symptoms related to cavernous sinus (CS) invasion. All the tumors were macroadenomas, and five of them (29%) had frank CS invasion. Two tumors showed evidence of a hemorrage (2 presented with apoplexy and 1 presented with visual deficit after a hemorrhage in a tumor cyst). The literature. Two tumors were considered incidental. Two tumors were treated with surgery and irradiation. Treatment options for unresetable or refractory meningiomas (chemotherapy and hormonal therapy) have been generally ineffective. Bevacizumab, a vascular endothelial growth factor receptor inhibitor, has been recently reported to have activity in these unresetable and refractory tumors (Puchner et al. Ann Oncol. 2010;21(12):2445). We report a case of a 41-year-old male with recurrent meningioma and pulmonary and metastases who achieved a partial response with bevacizumab. RESULTS: In 2007, a 41-year-old man presented with headaches, and he was found to have multifocal intracranial mass lesions by magnetic resonance imaging (MRI) evaluation. He underwent bifrontal craniotomy for resection of frontal and occipital meningiomas. In November 2009, he again developed headaches, and at that time, a brain MRI revealed at least three new lesions. Surgery was proposed. A preoperative chest x-ray showed evidence of bilateral metastatic lesions, and a lung biopsy revealed metastatic meningioma. In February 2010, the patient underwent gamma knife radiosurgery. From April 2010 until August 2010, the patient received 6 cycles of bevacizumab, weighing 70 kg every two weeks. No toxicity from surgery.
bevacizumab was observed. A followup computed tomography (CT) scan of the chest in August 2010 showed that the pulmonary index lesion had significantly decreased in size (4.6 cm x 2.9 cm to 3.0 cm x 1.9 cm), and the remaining pulmonary lesions demonstrated a 1-2 mm decrease in size. In December 2010, a CT scan showed a marked increase in the size of the lung metastases. CONCLUSION: Bevacizumab may have an important therapeutic role in the treatment of unresectable or refractory meningiomas and should be evaluated further.

NO-104. TREATMENT OF PRIMARY CNS LYMPHOMA: COMPARISON OF TWO HIGH-DOSE METHOTREXATE-BASED CHEMOTHERAPY REGIMENS

Jong Hee Chang, Jin Seok Kim, Jae Ho Cho, and Chang Ok Seo; Yonsei University College of Medicine, Seoul, Korea, Republic of Korea

Even though there is some convincing data that high-dose methotrexate-based chemotherapy regimens improve survival compared to previous controls treated with radiotherapy alone, the optimal treatment approach is still unclear. We retrospectively analyzed 31 primary CNS lymphoma (PCNSL) patients (25 men and 6 women) from January 2003 to March 2008. Nineteen patients (median age 55) received 2 courses of vincristine, methotrexate, doxorubicin, and cyclophosphamide (CHOP-BVAM) group. Grade 3 and higher hematological complications were significantly more common in the CHOP-BVAM group (21.4%) compared to the HD MVP group (3.6%). There were 3 patients with progression and 2 with relapse after treatment in HD MVP group and 3 relapses after treatment in CHOP-BVAM group. Grade 3 and higher hematological complications were significantly more common in the CHOP-BVAM group (21.4%) compared to the HD MVP group (3.6%). There were 3 patients with progression and 2 with relapse after treatment in HD MVP group and 3 relapses after treatment in CHOP-BVAM group. Grade 3 and higher hematological complications were significantly more common in the CHOP-BVAM group (21.4%) compared to the HD MVP group (3.6%).

NO-105. CYSTIC GLIOMAS ARE QUANTITATIVELY LESS AGGRESSIVE

Anne L. Baldock1, Russel Rockne1, Peter Canoll2, Donald Born1, Markus Bredel2, and James Chandler1; 1Northwestern University, Chicago, IL; 2Monmouth Medical Center, Long Branch, NJ

Gliomas are primary brain tumors with varying degrees of biological aggressiveness that invade normal brain tissue on a cellular level, which hinders treatment effectiveness. A subset of these lesions develops fluid-filled cysts. A recent study of 22 patients suggests that cysts in glioblastomas (GBMs) incur a significant survival advantage for these patients (Maldan, J Neurosurg 2004). We have observed a statistically significant survival advantage for cystic glioma patients (N = 32) compared to our age-matched control patient population (N = 44, p = 0.0139, Student’s t-test). We hypothesize that these two types of tumors must have different growth dynamics that lead to different prognoses for the same disease. Our patient-specific mathematical model for glioma kinetics extracts rates of net proliferation (p), net diffusion rate (D), and velocity of radial tumor growth from pre-treatment MRIs (T1Gd and T2). Because cyst fluid is not composed of proliferating tumor cells, we utilized a novel approach of cyst exclusion from one or both MRI modalities to allow estimation of the model parameters and tumor growth velocity. Cystic gliomas were found to have a statistically lower ratio of proliferation to inva-

NO-106. BCNU IMPREGNATED WAFER (GLIADEL) CHEMOTHERAPY-INDUCED BONE AND SCALP SARCOMA

Daniela Alexandru, Daniela Bota, and Mark E. Linskey; UCI Medical Center, Orange, CA

INTRODUCTION: Glioblastoma multiforme (GBM) has poor prognosis after recurrence. Treatment is challenging because chemotherapy does not penetrate the blood-brain barrier (BBB). However, a phase II trial of bevacizumab showed a median overall survival of 11 months. In 2008, we described a case of a 60-year-old woman with good performance (ECOG 1) at presentation. Because of its relative infrequency in older patients, the clinical characteristics of this disease are less well defined in adults than in children, and an optimal treatment regimen is not yet established for this tumor, and data in the literature are based on retrospective analysis rather than randomized studies because of the small number of adult patients with this disease. The optimal treatment regimen is not yet established for this tumor, and because of its rarity, cooperative multi-institutional clinical trials will be required to define the best treatment.

NO-107. 45-YEAR-OLD MAN WITH NEUROLOGIC DETERIORATION FROM MEDULLOBLASTOMA TREATED WITH TEMOZOLAMIDE

Joshua Nabie1 and Samul N. Ravali1; 1Monmouth Medical Center, Long Branch, NJ; 2Garden State Neurology & Neuro-Oncology, PC, West Long Branch, NJ

Medulloblastoma is a malignant CNS tumor that occurs primarily during childhood. It constitutes only 1% of all intracranial tumors in the adults. Because of its relative infrequency in older patients, the clinical characteristics of this disease are less well defined in adults than in children, and an optimal treatment regimen is not yet established. Complete tumor resection with cranial radiation is the standard of care for treatment of adult medulloblastoma. In contrast to childhood medulloblastoma, the role of chemotherapy in adult disease is undefined. Most of the studies in the literature are based on retrospective analysis rather than randomized studies because of the small number of adult patients with this disease. The optimal treatment regimen is not yet established for this tumor, and because of its rarity, cooperative multi-institutional clinical trials will be required to define the best treatment.

NO-108. A PHASE II TRIAL EVALUATING THE EFFECTS OF BORTezOmiB IN PATIENTS WITH RECURRENT MALIGNANT GLIOMAS TREATED PRIOR TO SURGERY AND THEN BORTezOmiB AND TEMOZOLOMIDE POSTOPERATIVELY

Jeffrey Rafter1, Sean Grimm1, Laurie Rice1, Joshua Rosenow1, Robert Levy1, Markus Bredel2, and James Chandler1; 1Northwestern University, Chicago, IL; 2University of Alabama, Birmingham, AL

INTRODUCTION: Bortezomib (Velcade), a second-generation proteasome inhibitor, has shown promising activity in a phase II trial of recurrent glioblastoma multiforme (GBM). The role of bortezomib in the context of a standard-of-care regimen for GBM remains undefined. The purpose of this study was to evaluate the safety and tolerability of bortezomib in combination with temozolomide in patients with recurrent glioblastoma multiforme.
BACKGROUND: NF-Kappa B is one of the mechanisms of resistance for malignant gliomas. A few trials have assessed bortezomib in the treatment of malignant gliomas with limited activity. This may be due in part to limitations in dose escalation caused by peripheral neuropathy. We performed a phase II trial with the goal of measuring bortezomib in tumor tissue and its effects on NF-Kappa B.

METHODS: Patients thought to be surgical can-cidates were enrolled after signing an IRB-approved consent form. They were treated with bortezomib 1.7 mg/m² IV on day 1, 4, and 8 and then had surgery on day 8 or 9. Approximately 14 days postoperatively, patients were started on temozolomide 75 mg/m² PO on days 1-7 and 14-21; on days 7 and 21, they received bortezomib 1.7 mg/m² (1 cycle for 1 month). Treatment continued until progression. If <1 patient had PFS 6 months, the trial would be stopped. RESULTS: 10 patients were enrolled (8 men and 2 women). Median age and KPS were 50 years (range 42-64) and 90% (range 70%-90%), respectively. Only 1 patient could not go on to surgery because of an extracranial hemangio and clinical deterioration. The median number of postoperative treatment cycles was 2 (range 1-4), with two patients removed from the study: one for infection (after 3 cycles, not restarted due to prolonged delays) and one for meningitis (after 2 cycles, withdrew from the trial). Six patients are deceased. The trial was stopped because no patient had a 6 month PFS. Tissue samples are currently being subjected to PK and NF-Kappa B analysis. CONCLUSION: Postoperative treatment with temozolomide and bortezomib did not have any activity in recurrent malignant gliomas. Tissue analysis is underway to determine if this is because of a lack of drug penetration or inability to inhibit NK-Kappa B sufficiently.

NO-109. AGGRESSIVE TREATMENT OF ATYPICAL/ANAPLASTIC MENINGIOMA

Pamela Z. New; Methodist Neurological Institute, Houston, TX

Atypical Grade II meningiomas comprise 20 to 35% of all meningiomas, and the 5-year survival rate has been reported from 28% to 61%. Anaplastic meningiomas, Grade III, comprise about 5 to 10% of these tumors and have an even poorer prognosis. There is no accepted method of treatment, and no chemotherapy has been found to be efficacious. Two cases of anaplastic meningioma and one atypical meningioma are presented. Case #1 is a 64 year old female who underwent resection of a right frontal-parietal atypical meningioma that recurred 3 months later. She then underwent intensity modulated radiotherapy (IMRT) and adjuvant temozolomide for one year and had no further recurrence after 76 months. Case #2 is a 55 year old female who underwent resection of an anaplastic meningioma that recurred one month later. She also underwent treatment with IMRT and adjuvant temozolomide for one year and has no further recurrence after 63 months. Case #3 developed a malignant transformation of a benign meningioma diagnosed 14 years earlier. Resection verified atypical meningioma, which was treated with IMRT and temozolomide and recurred 3 months later as a systemic anaplastic meningioma. There was no reoccurrence for 11 months. The patient’s survival after diagnosis of atypical pathology was 13 months, and death was due to widespread systemic disease. Improved treatments are needed for this aggressive type of tumor. Temozolomide and radiotherapy may be a reasonable protocol, especially when used early in the treatment phase, and it is well tolerated.

NO-110. INTRATUMORAL CONCENTRATIONS OF SUNITINIB AFTER ORAL ADMINISTRATION IN PATIENTS WITH HIGH GRADE GLIOMA

Scott R. Plotkin, Jeffrey G. Supko, William T. Curry, Andrew S. Chi, Eric V. Kramer, Anit Stemmer, Olofsson, and Tracy T. Batchelor; Massachusetts General Hospital, Boston, MA

INTRODUCTION: Sunitinib is an oral tyrosine kinase inhibitor of VEGFR1, VEGFR2, VEGFR3, PDGF receptor, c-KIT, and FLT-3 and is currently in clinical trials to assess its efficacy in malignant gliomas. In vivo studies of mice implanted with U87MG human glioma cells suggest that sunitinib achieves high concentrations in brain tumors. However, the penetration and distribution of sunitinib in high-grade gliomas in humans has not been determined. METHODS: Eight patients with progressive high-grade glioma for whom repeat surgical tumor debulking was clinically indicated after prior chemoradiation received sunitinib for 7 days prior to surgery (150 mg on day 1 and 50 mg on days 2-7). Patients resumed sunitinib treatment 14 days after surgery (50 mg daily on 4/2 weekly schedule) and continued treatment until disease progression or unacceptable toxicity. Tumor samples were collected during surgery, and plasma samples were obtained immediately before and after resection. The concentration of sunitinib in the plasma and tumor samples was determined using high performance liquid chromatography with mass spectrometric detection. RESULTS: The median patient age was 53 years, and 75% of patients were men. One patient experienced perioperative stroke and wound infection. Recurrent gliomas were noted in all but 1 sample, which was found to contain necrosis and treatment effect. This sample was excluded from pharmacokinetic analysis. The median concentration of sunitinib was 180.8 ng/g (range 55.5-911.8 ng/g) in the 7 tumor specimens and was 60.5 ng/ml (range 32.5 - 96.2l) in the paired blood samples. The median tumor-to-plasma ratio was 3.1 (range 1.0-20.5). Median time to progression on sunitinib was 72 days (range 17 to 199 days). CONCLUSIONS: These findings suggest that sunitinib achieves intratumoral concentrations higher than in plasma and penetrates the blood-brain barrier in high-grade gliomas. Tumor specimens are being analyzed separately to determine the pharmacology status of VEGFR2 and PDGF-Beta receptor.

NO-111. TREATMENT OF CEREBRAL RADIATION NECROSIS WITH BEVACIZUMAB: THE CLEVELAND CLINIC EXPERIENCE

Manmeet S. Ahluwalia, Neda Hashemi, Ganzefar Rahmatulla, Mital Patel, Sam T. Chao, David Ferreboom, Robert J. Weil, John H. Suh, Michael A. Vogelbaum, Glen H. Stevens, and Gene H. Barnett; Cleveland Clinic, Cleveland, OH

BACKGROUND: Radiation necrosis is a serious complication of radiation treatment for brain tumors. Therapeutic options including steroids, antiangiogenesis, and hyperthermia have not led to consistent benefit. It is postulated that radiation necrosis is postulated to be a continuous process involving endothelial cell dysfunction that leads to tissue hypoxia and necrosis with secretion of the vascular endothelial growth factor (VEGF). Bevacizumab, an antibody against VEGF, has been reported to reduce edema and improve the response to radiation necrosis. METHODS: After obtaining IRB approval, we used the Cleveland Clinic Brain Tumor and Neuro-Oncology Center’s database to identify patients who were treated with bevacizumab between 7/2007 and 1/2011 for radiation necrosis diagnosed on the basis of magnetic resonance imaging (MRI) and/or biopsy. RESULTS: 11 patients with a diagnosis of radiation necrosis (4 were biopsy proven) received bevacizumab. Post-treatment MRI was performed at an average of 8 weeks after initiating therapy with bevacizumab. Follow-up MRI demonstrated a radiographic response in all patients on the MRI fluid-attenuated inversion-recovery (FLAIR) sequences, and 10 of 11 patients showed improvement in the T1-weighted post-gadolinium contrast images. The average area change in the T1-weighted post-gadolinium contrast abnormalities was 33.7%, and the average change in the FLAIR images was 65% (using McDonald’s criteria). Ten patients showed clinical benefit. There was a mean daily dose reduction of 6.2 mg of dexamethasone after initiation of bevacizumab. CONCLUSIONS: Bevacizumab therapy appears to produce radiographic response as well as clinical benefit for patients with cerebral radiation necrosis.

NO-112. PATIENT-SPECIFIC MATHEMATICAL RADIATION ONCOLOGY: 4D OPTIMIZED DOSE DISTRIBUTIONS INFORMED BY GLIOMA KINETICS OF PROLIFERATION AND INVASION

David Corwin, Clay Holdsworth, Robert Stewart, Russ Rockne, and Kristin Swanson; University of Washington, Seattle, WA

A standard clinical radiation treatment for a glioblastoma consists of 60 Gy delivered on weekdays over 6 weeks (2 Gy per treatment day). Typically, radiation is applied to the T2 abnormality plus a 2 cm margin for 5 to 8 days. This one-size-fits-all approach does not explicitly account for tumor growth kinetics or the extent of hypoxia, which leads us to believe that the uniform doses applied in standard clinical treatments are suboptimal. A patient-specific mathematical model of glioblastoma utilizing the standard L-Q model [Rockey 2010] has been shown to predict untreated spatiotemporal proliferation and invasion of the tumor as well as the effect of clinical radiation therapy. We integrated this model with a multisite evolutionary algorithm that optimizes weekly dose distributions to maximize tumor cell killing [Holdsworth 2011]. Using the integrated model, simulated results demonstrate that the individualized plans optimized for tumor-specific biology can be much more effective in curbing tumor growth than current clinical treatment protocols while maintaining the same dose to normal tissue. Simulations for 3 patients with individualized dose distributions showed significantly different levels of effectiveness for individualized radiation treatments depending on the degree of radiosensitivity of the tumor. For highly radiosensitive tumors, a 50% increase in cell death was observed, whereas for radioreistant
NO-113. SEQUENTIAL TREATMENT WITH TEMOZOLOMIDE, PCV, AND RADIATION FOR GRADE II OLIGODENDROGLIOMAS
Jerome J. Grier and Thomas Kaley; Memorial Sloan Kettering Cancer Center, New York, NY

INTRODUCTION: The optimal treatment for low grade oligodendroglomas (LGO) is unknown, but radiation therapy (RT), temozolomide (TMz) and combination chemotherapy with PCV have shown efficacy. Most patients with LGO have prolonged survival and eventually receive multiple treatments. METHODS: We retrospectively assessed clinical course and outcomes in patients initially diagnosed with LGO who received both TMZ and PCV at any point. RESULTS: 25 patients were identified. Pure LGO histology was found in 19 (1p was deleted in 9, intact in 3, and its status unknown in 7) and mixed oligoastrocytoma in 6 (1p deleted in 3, and its status unknown in 3) patients. The median age of diagnosis was 43; 14 patients were female. Median PCV diagnosis was given in 5 patients (4 RT, 1 PCV). Median time to first treatment was 29 months (range 0-173 months). Median time to second treatment was 99 months (range 16-210 months). 21 patients also received RT at some point. Median overall survival was 147 months (range 67-340 months) with 9 patients still alive at last follow up (median 192 months, range 141-340). There was a clear trend for decreased progression free survival after subsequent treatments. There was a trend for longer progression free survival (median 81 months vs. 49 months for second treatment) after those initially treated with PCV compared to TMZ (57 months) and RT (65 months), but this did not reach statistical significance. Some partial responses to second or third treatments were observed in all groups: 1 patient received PCV after TMZ; 3 PCV after RT; 3 TMZ after PCV; 3 RT after PCV. By Kaplan-Meier analysis with censoring, there was no significant difference in overall survival between patients initially treated with PCV versus those treated with TMZ or RT, although the numbers were small. Conclusions are limited by the retrospective, uncontrolled nature of the study and small numbers of patients.

NO-114. PREDICTIVE INTEGRATION OF TUMOR GROWTH KINETICS ON CLINICAL IMAGING WITH HISTOLOGICAL FEATURES THROUGH PATIENT-SPECIFIC SIMULATION
Russell C. Rockne1, Alexander R. Anderson2, and Kristin R. Swanson1;
1University of Washington, Seattle, WA; 2Moffitt Cancer Center, Tampa, FL

INTRODUCTION: Gliomas are heterogeneous primary brain neoplasms that can progress from low-grade to high-grade (glioastoma). Although low-grade gliomas involve low degrees of angiogenesis, glioblastomas are considered highly angiogenic. This suggests that interactions between glioma cells and the tumor microenvironment play an important role in aggressive tumor formation and progression. The dynamics of these interactions connecting tumor growth rates and histological features are not well explored in individual patients. Using a mathematical model, we have successfully integrated clinical imaging and histopathology to predict imaging and histological features on a patient-specific basis. METHODS: To quantitatively explore tumor-microenvironment interactions, we modeled the interactions of normoxic glioma cells, hypoxic glioma cells, vascular endothelial cells, diffusible angiogenic factors, and necrotic activity, all hallmark of the histological diagnosis of glioma. Patient-specific model parameters were computed from pretreatment magnetic resonance imaging (MRI) and used to calibrate the model. Patient-specific simulations integrated multiplicity imaging with histopathology for 8 glioblastoma patients. Model-simulated predictions were compared to histologic tests including WHO grade, Ki67 proliferation index, mitotic activity, and HIF1alpha ALLRED score as well as the size of the necrosis and contrast-enhancing volume on MRI. RESULTS: Model simulations quantitatively predicted the spectrum of in vivo dynamics of gliomas visualized with medical imaging for features that characterize increasing degrees of “malignancy,” which include the degree of cellularity, mitoses, hypoxia-induced neo-angiogenesis, and necrosis. Model predictions of histological and imaging features across 8 patients fell within 3 standard deviations of the mean for a preponderance of those tested. This indicated that the model is capable of integrating tumor kinetics and histology across a wide range of tissue and imaging scale heterogeneity. This provides a novel tool for bridging macroscopic measures of tumor growth with microenvironment-driven histological features and thus providing unique predictive insight into each patient’s tumor through an in silico virtual control.

NO-115. PACLTAXEL POLIGLUMEX (PPX), TEMOZOLAMIDE (TMZ) AND RADIATION (RT) FOR NEWLY DIAGNOSED HIGH-GRADE GLIOMA: A BROWN UNIVERSITY ONCOLOGY GROUP (BRUOG) PHASE II STUDY
Survi Jayavelan1, Marc Goldman1, Jerry Boxerman1, John Donahue1, Heinrich Einzinger1, Devon Evans1, Brigid O’Connor1, M Yakub Puthawala1, A. K. Veleles1, Deus Cade1, Vernis Blisset1, Mavey Dahn1, L. Alyson Santullianni1, Maria Constantino1, Thomas DiPietro1, and Howard Safran1; Rhode Island Hospital, Providence, RI; 2Maine Medical Center, Portland, ME

BACKGROUND: Paclitaxel poliglumex (PPX) is drug conjugate that links paclitaxel to a polyglutamic acid polymer, which results in an increased radiati...
NO-117. THE CLINICAL APPLICATION OF 2-HYDROXYGLUTARATE (2HG) IN THE MANAGEMENT OF IDH-MUTATED GLIOMAS
Elizabeth A. Maher, Sandeep Ganji, Ralph DeBerardinis, Kimmo Hatanpaa, Dinesh Rakheja, Xiao-Li Yang, Tomoyuki Mashimo, Jack Raisanen, Christopher Madden, Bruce Mickey, Craig Malloy, Robert Bachoo, and Changho Choi; University of Texas Southwestern Medical Center, Dallas, TX

Isocitrate dehydrogenase converts isocitrate to alpha-ketoglutarate (alphaKg) in the cytosol (IDH1) and mitochondria (IDH2). The identification of mutations in IDH1 and IDH2 among the majority of patients with WHO grade II and III gliomas has directed attention to the role of abnormal metabolism in the pathogenesis and progression of these tumors. The mutations are confined to the active site of the enzyme and result in a gain of function that causes the mutant enzyme to produce D-2-hydroxyglutarate (2HG). This metabolite, normally present in vanishingly small quantities, can be elevated by orders of magnitude in gliomas harboring IDH1 or IDH2 mutations. Although the metabolic consequences and downstream molecular effects of these mutations have yet to be elucidated, their potential value as diagnostic and prognostic markers in gliomas has been established from their clear association with improved overall survival when outcomes are compared between IDH-mutant and IDH wild-type tumors. We have an enrolling IRB-approved clinical protocol to develop multiparametric magnetic resonance spectroscopy (MRS) at 3Tesla for low abundant metabolites in patients with gliomas. Using optimized point-resolved spectroscopy (PRESS) and difference editing sequences, we have detected 2HG in vivo by MRS. When our technique was applied to tumors in 30 patients with all grades of malignant gliomas, we achieved 100% sensitivity and specificity. For each case in which 2HG was detected by MRS, an IDH2 or 2 mutation in the tumor was confirmed by DNA sequencing. Failure to detect 2HG by MRS was associated with the detection of wild type IDH1 and 2 in each case. Data will be presented showing the sensitivity of 2HG in detecting tumor progression and correlating 2HG levels with response to treatment. The ease with which 2HG measurement could be incorporated into standard MR imaging suggests that it may be an important biomarker in the clinical management of IDH mutated gliomas.

NO-118. TREATMENT OF PINEAL GLOBLASTOMA WITH LEPTO MENCEAL METASTASES: CASE REPORT
Tuilka Rangan and Noor Yono; North Shore LIJ HS, NY, NY

Glioblastoma multiforme (GBM) is the most common primary malignancy of the central nervous system. Pinea glioblastomas (GBM) are exceedingly rare tumor with very poor prognosis. Only 18 cases so far have been reported in the literature. We present a case of pineal gland GBM with leptomeningeal disease successfully treated with chemotherapy and radiation. A 35 year old man presented with progressive headache and Parinaud syndrome. Brain MRI showed an enhancing pineal mass with hydrocephalus. The patient had a biopsy done along with a ventricular-peritoneal shunt placement. The pathology was consistent with GBM with a Ki-67 labeling index of 30-50%. The patient was readmitted within 2 weeks of biopsy with worsening of Parinaud syndrome and the development of peduncular hallucinations. Repeat brain and total spine MRI showed an increase in the size of the pineal lesion (measuring 2.6 X 2.5 X 2.8 cm) and diffuse linear leptomeningeal disease. Chemotherapy with temozolomide at 150mg/m2 was started. On day 3 of temozolomide treatment, the patient developed cauda equina syndrome. High-volume lumbar puncture was performed, and he received one dose of intrathecal methotrexate. Within 24 hours following the methotrexate treatment, the patient showed significant improvement of the cauda equina syndrome. Initial lumbar puncture showed a markedly elevated protein count of 2456, cytology was negative, and WBC counts were within normal limits. High-volume lumbar puncture was repeated with intrathecal methotrexate two days apart. Two weeks of hyperfractionated radiation therapy to the pineal lesion with concurrent temodar was given. The patient had significant improvement of peduncular hallucinations and Parinaud syndrome after the radiation. He was further treated with avastin every 2 weeks and monthly temozolomide (5/23). The followup brain MRI after two months of treatment showed that his pineal mass size has decreased to 1 X 1.5 X 1.2 cm, and his CSF protein level has improved to 315.

NO-119. UTILITY OF CEREBROSPINAL FLUID CYTOMETRY IN THE DIAGNOSIS OF NEOPLASTIC MENINGITIS
Omar Zalatimo, Christina Zoccoli, and Michael Glantz; Penn State Hershey Medical Center, Hershey, PA

BACKGROUND: Cerebrospinal fluid (CSF) is a valuable diagnostic tool in patients with cancer. However, this test is of limited utility when not guided by clinical judgment. METHODS: Retrospective analysis of CSF cytology for detection of carcinomatous meningitis was performed. The determination of the utility CSF cytology was based on a previously determined clinically significant difference between the pretest probability of disease and the post-test probability. Patients without cancer (n = 403), patients with known cancer without suspicion of neoplastic meningitis (NM) (n = 41), and patients with known cancer and suspected NM (n = 81) were analyzed separately. Costs incurred by uninformative testing were estimated for CSF cytology, culture, glucose, and protein levels. RESULTS: The positive likelihood ratio (LR+ ) and negative likelihood ratio (LR-) for CSF cytology were >10^3 and 0.33, respectively, in patients without known cancer. Because the prevalence (pretest probability) of NM in this cohort was already very low (0.7%), a negative test decreased the probability of NM to 0.2% (post-test probability). In patients with known cancer, LR+ was 24.3, and LR- was 0.29. A positive test increased the likelihood of NM from 15% to 81%, and a negative test decreased the likelihood of NM to 5%. In patients with known cancer and suspected NM, LR+ was >10^3, and LR- was 0.048. A positive test increased the likelihood of NM from 26% to 100%, and a negative test decreased the likelihood to 1.6%. The percentage of performed tests that were uninformative (true negative) was 99%, 80%, and 74% for patients without cancer, patients with cancer without suspicion of NM, and patients with known cancer, respectively. These uninformative tests had a total cost of $110,432. CONCLUSIONS: In patients without known cancer, routine CSF cytology is uninformative, inefficient, and costly. In patients with known cancer but without suspicion of NM, routine CSF cytology is more informative and cost effective. In patients with known cancer and suspected NM, CSF cytology is most informative, and its routine use can be justified.

NO-120. ANAPLASTIC GANGLIOGLIOMAS: REPORT OF 3 CONFIRMED CASES
Seungjo J. Han, Matthew Sun, Mitchel S. Berger, Manish Aghi, Nalin Gupta, and Andrew T. Parsa; UCSF, San Francisco, CA

Anaplastic gangliogliomas (AGGs) are rare tumors, and published clinical experience with them is limited to case reports and series. Consequently, their clinical and biologic behavior are poorly understood. Here, we present a series of 3 patients with pathologyConfirmed AGGs. Patients were identified through the UCSF department of pathology database (1985-2010). AGG patients represented 2.1% of all patients diagnosed with ganglioglioma of all grades during this time. All three patients had a prior diagnosis of low grade ganglioglioma (LGGG); in two cases, histologic review revealed regions of hypercellularity and scattered mitoses. A 15-year-old girl underwent further surgery after LGGG resection because of the above concerns on pathology. She received adjuvant external beam radiation followed by temozolomide. She is currently alive 7 years after diagnosis. A 25-year-old patient who presented with seizures had radiographic progression 1 year after LGGG resection and received gross total resection followed by external beam radiation. He is alive after 10 years. A 40-year-old man presented with intraparenchymal hemorrhage and suffered bilateral ACA infarcts and hydrocephalus. His tumor progressed 8 months after initial resection, upon which time another resection was performed followed by radiation and temozolomide. He died 7 months after diagnosis because of steady neurological decline and seizures. Although the literature commonly shows that AGGs progress from prior LGGGs, it is interesting that in our series, all three patients had prior subtotally resected LGGGs, which raises the possibility that LGGGs may progress to AGGs if not completely resected. Undersampling may have been present as well, which was suggested by higher-grade features seen on pathology review. Our series suggests and underscores the importance of achieving gross total resection to ensure that gangliogliomas are not misdiagnosed AGGs and to potentially prevent progression of LGGGs to AGGs. Patients with AGGs may have favorable long-term survival when managed with aggressive resection followed by adjuvant radiation and/or chemotherapy.