PC-01. PHASE I AND PHARMACOKINETIC TRIAL OF PTC299 IN PEDIATRIC PATIENTS WITH REFRACTORY OR RECURRENT CNS TUMORS: A PBTC STUDY
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BACKGROUND: PTC299 is a novel, orally bioavailable small molecule that selectively inhibits vascular endothelial growth factor receptor protein synthesis at the post-transcriptional level. METHODS: A phase 1 and pharmacokinetic study was performed in children aged 3-21 years, inclusive, with recurrent brain tumors. PTC299 was given 2-3 times per day every day based on body weight. Six patients were enrolled at each dose level. Four dose levels were planned, beginning at 1.2 mg/kg/dose ID at 2.0 mg/kg/dose ID, escalation was based on tolerability and mandatory pharmacokinetic data. RESULTS: A total of 28 patients (median age 11.6 years [range 3.5-21.1]) were enrolled, with a wide variety of tumors including 8 low-grade gliomas, 9 high-grade gliomas, and 4 brainstem gliomas; 21 patients were evaluable for toxicity. One dose-limiting toxicity (DLT) possibly related to treatment (hyponatremia) was identified during the first course of treatment. Possibly related grade 3 toxic effects of hyponatremia (1), hypertension (1), and lethargy (1) were noted with prolonged use. Pharmacokinetic analysis in cycle 1 demonstrated the expected rise in drug concentrations with increasing doses. Concentrations at dose level three were similar to adult phase II levels. With prolonged use, some patients had drug accumulations without associated toxicity. Objective radiographic responses were not seen, but prolonged (greater than 6 months) stable disease was seen in 5 of 8 patients with low-grade gliomas, 2 of whom maintained disease control for more than 1 year. Four evaluable patients were entered at dose level 4, but the study was suspended pending evaluation of toxicity seen in the adult trials. CONCLUSIONS: PTC299 was well tolerated and prolonged disease control was seen in children with low-grade gliomas. Further study, possibly in combination with other agents, is reasonable, although the pharmacokinetic profile may be challenging, and the adult toxicity profile must be taken into account.

PC-02. CNS INJURY, NEUROCOGNITIVE, AND QUALITY OF LIFE OUTCOMES IN CHILDREN WITH BRAIN TUMORS TREATED WITH CHEMOTHERAPY
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Two-thirds of children with brain tumors achieve long-term survival. Increasingly, children younger than 5-6 years at diagnosis are treated with high-dose chemotherapy, delaying or foregoing cranial irradiation. Systemic administration of chemotherapy is associated with damage to healthy brain tissue, but these effects in children with brain tumors are unclear. Our first objective was to compare structural neural integrity with the post-transcriptional level. METHODS: A phase 1 and pharmacokinetic study was performed in children aged 3-21 years, inclusive, with recurrent brain tumors. PTC299 was given 2-3 times per day based on body weight. Six patients were enrolled at each dose level. Four dose levels were planned, beginning at 1.2 mg/kg/dose ID and escalated to 2.0 mg/kg/dose ID. Escalation was based on tolerability and mandatory pharmacokinetic data. RESULTS: A total of 28 patients (median age 11.6 years [range 3.5-21.1]) were enrolled, with a wide variety of tumors including 8 low-grade gliomas, 9 high-grade gliomas, and 4 brainstem gliomas; 21 patients were evaluable for toxicity. One dose-limiting toxicity (DLT) possibly related to treatment (hyponatremia) was identified during the first course of treatment. Possibly related grade 3 toxic effects of hyponatremia (1), hypertension (1), and lethargy (1) were noted with prolonged use. Pharmacokinetic analysis in cycle 1 demonstrated the expected rise in drug concentrations with increasing doses. Concentrations at dose level three were similar to adult phase II levels. With prolonged use, some patients had drug accumulations without associated toxicity. Objective radiographic responses were not seen, but prolonged (greater than 6 months) stable disease was seen in 5 of 8 patients with low-grade gliomas, 2 of whom maintained disease control for more than 1 year. Four evaluable patients were entered at dose level 4, but the study was suspended pending evaluation of toxicity seen in the adult trials. CONCLUSIONS: PTC299 was well tolerated and prolonged disease control was seen in children with low-grade gliomas. Further study, possibly in combination with other agents, is reasonable, although the pharmacokinetic profile may be challenging, and the adult toxicity profile must be taken into account.

PC-03. COMPARISON OF THE INCIDENCE AND TIME OF ONSET OF THYROID DYSFUNCTION IN PATIENTS WITH MEDULLOBLASTOMA TREATED WITH PROTON OR PHOTON CRANIOSPINAL IRRADIATION
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The use of protons for craniospinal irradiation (CSI) for children with medulloblastoma theoretically diminishes the exposure of adjacent normal tissue to radiation. However, the impact of proton therapy on the incidence and timing of treatment-related thyroid dysfunction is uncertain. This study compared the incidence of hypothyroidism between children treated with CSI using protons and photons. Patients were divided into two cohorts: those treated with CSI using protons (n = 55) or photons (n = 11). The mean age was 8.32 years (range 1.28 to 20.61). The mean follow-up time was 10.26 years (median 11.46 vs. proton 5.15). Two high-risk patients were treated with photons (18.2%), and 12 high-risk patients were treated with photons (21.8%). Thyroid dysfunction was significantly less likely (2-sided p = 0.002) in children treated with proton CSI (9.0%) than in those treated with photon CSI (58.18%). The mean time to the onset of thyroid dysfunction in patients treated with photons (CSI 3.49 years) did not reach statistical significance (2-sided p = 0.242). In conclusion, the use of proton CSI is associated with a lower incidence of hypothyroidism, most likely related to a lower radiation dose to the thyroid gland.

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INTRODUCTION: Incomplete tumor resection carries a poorer prognosis in childhood medulloblastoma (MB) and other central nervous system primitive neuro-ectodermal tumors (PNETs). Whether delayed gross total resection after chemotherapy improves this prognosis is not known. We evaluated the impact of “second-look” surgical resections on the outcome of children with MB and PNETs with persistent residual disease after induction chemotherapy. We sought to determine whether such delayed attempts at achieving complete resections improved the ultimate event-free survival (EFS) of these patients. METHODS: A total of 183 patients (MB = 122 and PNET = 61) were enrolled in Head Start II and III between 1997 and 2009. Eighty children initiated chemotherapy with residual tumor (MB = 54 and PNET = 26). Of these patients, 29 had metastatic disease (MB = 16 and PNET = 13). At the end of induction chemotherapy, 42 patients had persistent residual tumor (MB = 24 and PNET = 18); 9 of these patients underwent “second-look” surgical resections (MB = 7 and PNET = 2). The Wilcoxon-Breslow-Gehan test was performed for comparison of the pertinent patient subgroups, and the 2-year EFS rates are provided. RESULTS: For the 42 patients with persistent disease after induction chemotherapy, the 2-year EFS was 43 +/− 9.1%; for those undergoing second-look surgery (n = 9) the 2-year EFS was 86.6 +/− 18.6%; and for those not undergoing second-look surgery (n = 33), the 2-year EFS was 38.2 +/− 9.8% (p = 0.19). For MB patients with residual disease, the
2-year EFS was 54.8 ± 12.2% for those undergoing second-look surgery (n = 7), the 2-year EFS was 80.0 ± 17.9% for those not undergoing second-look surgery (n = 17), the 2-year EFS was 49.0 ± 17.9% for those patients who had a diagnosis of HSOS, the 2-year EFS was 29.5 ± 12.5% for those undergoing second-look surgery (n = 2), the 2-year EFS was 50.0 ± 35.4% and for those not undergoing second-look surgery (n = 16), the 2-year EFS was 25.4 ± 13.5% (p = 0.39).

CONCLUSIONS: Second-look surgical resection was used in only 20% of eligible patients. There was a nonsignificant trend toward improved outcomes for these patients. Selection bias cannot be excluded as an explanation for this trend. Further study using a multinational meta-analysis is warranted.

PC-05. FINAL REPORT OF OUTCOME OF THE CCG-99703 CHILDREN’S ONCOLOGY GROUP STUDY FOR CHILDREN LESS THAN 3 YEARS OF AGE NEWLY-DIAGNOSED WITH MALIGNANT BRAIN TUMORS
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INTRODUCTION: The outcome for young children (<3 years of age) newly diagnosed with malignant brain tumors remains poor. The primary goals of the CCG-99703 prospective single-arm trial of chemotherapy alone were to assess the feasibility and tolerability of, as well as the response rate to, this novel intensive regimen and have been reported previously. We now report on the long-term outcome of these patients. METHODS: Between March 1998 and October 2004, 92 patients were enrolled, and 92 were deemed eligible on central review. Following surgical biopsy/resection, patients were to undergo three identical cycles of induction chemotherapy (vincristine, cyclophosphamide, etoposide, and cisplatin) administered over 3 days every 21-28 days. Patients without tumor progression were to undergo three identical cycles of myeloablative chemotherapy (thiotepa and cyclophosphamide). This sequence would be repeated three times to primary cellular/classic ependymoma, but with areas of necrosis and increased mitotic activity, resulting in a downgrade to a final WHO classification of grade III. Anaplastic ependymoma. The child made an uneventful recovery from neurosurgery and is receiving chemoradiotherapy in a clinical trial.

CONCLUSIONS: Large expansile supratentorial ependymomas can cause significant mass effect with resultant signs of increased intracranial pressure. Graft/host reaction is extremely unusual in pediatric intracranial neoplasms. Our unusual case, a large hemispheric tumor likely presented for many months or years before diagnosis, suggests that ependymoma can lead to significant overlying bone changes and extension of tumor beyond the central nervous system space. The physiologic explanation for this finding is uncertain but may be related to “pressure atrophy” of bone or perhaps cytokine-mediated trabecular bone dissolution. We recommend further reporting of such cases.

PC-07. ATYPICAL NEUROIMAGING IN PEDIATRIC SUPRATENTORIAL ANAPLASTIC EPENDYMOMA
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INTRODUCTION: Ependymoma is the third most common pediatric central nervous system tumor. Most tumors arise intracranially, usually in children younger than age 5. Typical computed tomography (CT) and magnetic resonance (MR) imaging features include intratumoral calcification or contrast enhancement and T1 iso-/hypointense to surrounding brain parenchyma. We present a rare case of significant bone erosion and extracranial extension of tumor. METHODS: An 11-year-old girl presented with a 6-month history of headaches, strabismus, and a growing “lump behind her ear.” She also had evidence of developmental slowing and toe-walking over the preceding several years. RESULTS: CT and MR scanning revealed a 9.7 × 8.7 × 7.7-cm heavily calcified hemispheric mass causing transfrontal and transtentorial herniation, ventricular trapping, and peritumoral edema. Diffusion restriction was evident, and multivessel crowding due to mass effect was seen. Erosion of the overlying calvarium with exophytic protrusion of tumor extracranially was remarkable. A near-total resection of the large mass was accomplished using conventional microsurgical dissection and intraoperative MR scanning. Histopathology revealed a primarily cellular/classic ependymoma, but with areas of necrosis and increased mitotic activity, resulting in a downgrade to a final WHO classification of grade III, or anaplastic ependymoma. The child made an uneventful recovery from neurosurgery and is receiving chemoradiotherapy in a clinical trial.

CONCLUSIONS: Large expansile supratentorial ependymomas can cause significant mass effect with resultant signs of increased intracranial pressure. Graft/host reaction is extremely unusual in pediatric intracranial neoplasms. Our unusual case, a large hemispheric tumor likely present for many months or years before diagnosis, suggests that ependymoma can lead to significant overlying bone changes and extension of tumor beyond the central nervous system space. The physiologic explanation for this finding is uncertain but may be related to “pressure atrophy” of bone or perhaps cytokine-mediated trabecular bone dissolution. We recommend further reporting of such cases.

PC-08. RADIATION-INDUCED SECOND MALIGNANCIES IN TWO LONG-TERM SURVIVORS OF MEDULLOBLASTOMA: CASE REPORT AND REVIEW OF THE LITERATURE
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Children diagnosed with medulloblastoma may experience a cure rate of over 80% in nonmetastatic and non-anaplastic subtypes and improved survival in metastatic and/or anaplastic histological subtypes. Standard therapy involves a maximal safe resection, irradiation, and adjuvant chemotherapy. While the most likely cause of death is recurrence, there is a growing increase in treatment morbidity and mortality related to second malignant neoplasms and chemotherapy-induced tumors of the central nervous system, including meningoforms but more importantly are high-grade astrocytomas, specifically grade 4. We report the case histories of two pediatric patients treated for medulloblastoma who developed secondary brain tumors 7 and 13 years, respectively, after their initial diagnosis. Both patients were asymptomatic at the time of the magnetic resonance scans that revealed multifocal tumors in one case and a solitary lesion in the other. The pertinent radiographic and pathologic information will be presented, and a review of the literature will be discussed.
PC-09. METRONOMIC AND TARGETED ANTI-ANGIOGENESIS THERAPY FOR CHILDREN WITH RECURRENT MEDULLOBLASTOMA

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Patients with relapsed medulloblastoma have a bleak prognosis irrespective of the salvage therapy used. An evolving alternative approach to conventional chemotherapy is targeting neovascularization by interfering with tumor angiogenesis at various levels. We report on an update and extended survival of 69 patients with recurrent medulloblastoma treated with an antiangiogenic combination therapy partly included in a previous publication.

METHODS: From November 2006 to April 2011, nine consecutive children with recurrent medulloblastoma (6 first recurrence, 3 multiple recurrences) started treatment with an antiangiogenic multidrug regimen (bevacizumab, thalidomide, celecoxib, folicnibrate, etoposide, and cyclophosphamide) augmented with intraventricular therapy (etoposide and liposomal cytarabine) in seven patients. All patients had received craniospinal irradiation and prior multigang chemotherapy, including HDCT in one. The median age at the start of antiangiogenic therapy was 14 years (range 7-24). For their current relapse, four patients received antiangiogenic therapy only, and five patients received some additional therapy (reoperation, local radiotherapy, or chemotherapy). RESULTS: As of May 2012, 6 of 9 patients are alive at a median follow-up of 30 months. Two patients died of tumor progression 63 and 10 months after their last recurrence. One patient died of an accident without signs of tumor progression on MRI 23 months after the initiation of target therapy. The remaining six patients are alive, with a median follow-up times of 44, 40, 40, 19, 14, and 12 months, respectively, and three of them have been off therapy for 25, 9, and 5 months, respectively. Overall and event-free survival after 6 months was 100%, after 12 months 85%, and after 24 months 68 ± 19%. Therapy was generally welltolerated; toxicities were manageable; and quality of life was considered better than with previous therapies with regard to participation in daily life. CONCLUSIONS: Our results suggest that antiangiogenic metronomic chemotherapy has clinical activity in recurrent medulloblastoma. Further investigation with a formal phase II study is in progress (Memmatal; ClinicalTrials.gov Identifier: NCT01356290) and will be extended internationally.

PC-10. MD ANDERSON EXPERIENCE WITH PEDIATRIC PILOCYTIC ASTROCYTOMA: DIFFERENT LOCATION, DIFFERENT OUTCOME

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BACKGROUND: Pilocytic astrocytoma (PA), the most common gloma in the pediatric population, is commonly infratentorial. We present the clinical experience at MD Anderson Cancer Center of 117 patients to match clinical presentation with clinical outcome. METHODS: We conducted an IRB-approved retrospective review of patients 18 years or younger with PA at The University of Texas MD Anderson Cancer Center during the past 17 years. RESULTS: We reviewed 117 patients with PA (19 with NF1; 13 familial history; 34 were incidental; median age at diagnosis: 12 years) seen between 1995 and 2012 and included 112 of those with confirmed diagnosis. Anatomically, there were 53% suprasellar and 42% posterior fossa. The most common symptoms at presentation were visual dysfunction, headache, and vomiting. Patients were followed up for a median of 16 years; at last follow-up, 100 patients were alive, and 15 patients were deceased. Five patients had disease dissemination after diagnosis. Upfront treatment of the suprasellar PA patients ranged: 35% subtotal resection (STR) plus adjuvant chemotherapy (95% progressed), 14% STR plus adjuvant radiotherapy (RT) (75% progressed), 16% STR only (89% progressed), and 14% gross total resection (GTR) still stable at 114 months. Upfront treatment of posterior fossa PA patients ranged: 83% GTR stable at median 5.75 years, 35% STR (78% progressed), 26% STR plus adjuvant chemotherapy (75% progressed), and 10% STR plus adjuvant RT (33% progressed). CONCLUSIONS: This retrospective analysis compared PA anatomical locations with respect to clinical outcomes. Our clinical experience confirms overall and progression-free survival to be better in posterior fossa PAs. In this cohort, GTR was optimal, but STR with adjuvant RT was second best especially in posterior fossa tumors. This analysis suggests there is a difference in clinical outcome according to anatomical location, and as part of our ongoing study, we will investigate the molecular behaviors in these locations.

PC-11. INTRACRANIAL ATYPICAL TERATOID RHABDOID TUMOR: CLINICO-PATHOLOGICAL STUDY FROM NORTH INDIA

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Pediatric supratentorial tumors are challenging because of their unique location, varied pathologies, and imaging characteristics. Oligodendrogliomas, craniopharyngiomas, and germinomas have all distinctive features. The cystic lesions may not be so clear. Treatment aims at decompressing the brain. Medical records of 14 patients with Dx: ATRT were reviewed. Median age at presentation was 5 years (range 0.8-8 years). Presenting complaints included vomiting (75%), headache (50%), orbital symptoms (41.67%), motor impairment (25%), and gait abnormalities (16.67%). On contrast-enhanced MRI, two tumors were supratentorial in 38.33% of patients and infratentorial in 41.67% of patients. Cystic component, contrast enhancement, and hydrocephalus were noted in 75% of patients each, and calcification was noted in 41.67% of patients. All patients underwent tumor resection: gross total resection (25%), near-total resection (16.67%), and subtotal resection (58.33%). Histopathology confirmed AT/RT with MB-1 labeling index varying from 11% to 85% (median 52.5%). There was lack of immunostaining for INI1, suggesting INI1 mutation. The majority of tumors exhibited immunopositivity for EMA (91.67%), synaptophysin (75%), cytokeratin (66.67%), vimentin (58.33%), SMA (50%), and GFAP (50%). Adjuvant radiation (36 Gy/20/4/weeks) to the entire neuraxis followed by a local boost of 20 Gy/10/2weeks was started in 5 patients and completed in 4 patients (33.33%). Systemic chemotherapy was administered in 7 (58.33%) patients and FA/MTX-resistant and of such as p16 (3.33%), with VAC (vincristine, dactinomycin, cyclophosphamide) being the most common regimen (33.33%). Median overall survival was 22.6 months. At last follow-up, 2 patients had complete response, 5 patients are alive with evidence of disease, and 7 patients expired of disease progression. Median survival of 22.6 months reflects the aggressive biology of this rare neoplasm.

PC-12. MALIGNANT TRANSFORMATION OF GROWING TERATOMAS: A GROWING PHENOMENON

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INTRODUCTION: Growing teratoma syndrome (GTS) occurs in about 5% of pediatric intracranial germ cell tumors, and up to 20% of non-germnomatous germ cell tumors (NGGCT) progress to GTS following chemotherapy. The growing teratoma is thought to arise from the chemotherapy-resistant, teratomatous portion of a germ cell tumor. This component is commonly benign but may undergo malignant transformation. METHODS: We present two pediatric patients whose intracranial NGGCTs progressed to GTS during chemotherapy and later transformed to malignant NGGCTs after partial resection and irradiation. The initial tumors were diagnosed by MRI scans and elevated serum and CSF markers. Despite the normalization of tumor markers with chemotherapy and partial decreases in tumor volume, subsequent imaging showed disease progression. Subtotal resection was performed, and pathology revealed benign teratoma. Radiotherapy was administered. RESULTS: Several years following this treatment, further growth was seen on surveillance scans. Re-resection was performed. Pathology indicated malignant carcinoma in one patient and sarcoma in the other. The patient with carcinoma received palliative care, and the patient with sarcoma underwent further resection, intensive chemotherapy, and an autologous stem cell transplant and is currently in remission (16 months). CONCLUSIONS: Malignant transformation of presumed residual teratoma has been reported in only a handful of cases. Treatment of NGGCT involves platinum-based chemotherapy with craniopinal irradiation and a boost to the primary site, with cure rates of around 80%. Teratomas are characteristically radioresistant, and teratoma component of malignant teratoma is thought to be chemoresistant. In the event that residual or growing teratoma is suspected, complete resection should be considered early in the management, as there may be a significant risk of malignant transformation of the teratoma.
PC-14. NEUROLOGIC COMPLICATIONS OF PEDIATRIC CANCER: THE MSKCC EXPERIENCE

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INTRODUCTION: Pediatric cancer patients undergo a variety of therapies, including surgery, chemotherapy, and irradiation; as such, they also experience a unique set of side effects. We sought to review the neurologic complications these patients experience. METHODS: After obtaining IRB approval, we identified patients treated in the Pediatrics Department at Memorial Sloan-Kettering Cancer Center who received a neurologic consultation from January 2007 to August 2011. Patient demographics, reason for the consultation, primary diagnosis, status, and neurologic complications were recorded in the CAISIS (MSKCC data management system) neurologic consultation database. A total of 574 records were reviewed, with an average of 3.2 visits per patient. RESULTS: Headache, seizure, opsoclonus-myoclonus-ataxia (OMA) syndrome, encephalopathy, and weakness were the most common reasons for consultation across all patients. Consultations were most commonly in patients with CNS tumors (40%) followed by those with leukemia (13%), sarcoma (9%), and lymphoma (2%). Patient mortality was the highest in the 6 months post consultation in all patients. Conclusions: Neurologic complications are common in pediatric cancer patients; headaches and seizures may portend poor survival.

PC-15. HIT-GBM-D: HIGH-DOSE METHOTREXATE FOR PEDIATRIC HIGH-GRADE GLIOMA

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Methotrexate (MTX) is a folate antagonist. The drug was tested in the treatment of high-grade glioma in a randomized prospective phase III study. The patients received two cycles of MTX 5g/m² over 24 hours post resection and radiation therapy. Excision rates with excellent visual improvement and significant decreases in neuro-endocrine morbidity.

PC-16. A PHASE I TRIAL OF MK-0752 IN PEDIATRIC PATIENTS WITH RECURRENT OR REFRACTORY CNS MALIGNANCIES: A PEDIATRIC BRAIN TUMOR CONSORTIUM STUDY

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BACKGROUND: The NOTCH pathway plays a central role in normal neural stem cell regulation and maintenance. NOTCH signaling is also important in medulloblastoma pathogenesis; NOTCH amplification has been identified in a subgroup of posterior fossa ependymomas, and high levels of NOTCH ligand expression have been identified in high-grade gliomas. MK-0752 is an orally active inhibitor of gamma secretase (IC50 of 55 nM). A phase I trial of weekly MK0752 was conducted in children with recurrent CNS malignancies to estimate the maximum tolerated dose (MTD), dose-limiting toxicities (DLTs), and expression of NOTCH and HES proteins in peripheral blood mononuclear cells (PBMCs) prior to and following treatment with MK-0752. METHODS: MK0752 was administered once weekly at dose levels of (1) 1000 mg/m² and (2) 1400 mg/m² dose using the rolling 6 design. PK analysis was performed during the first course. RESULTS: We enrolled 10 eligible patients (6 males, median age 8.8 years [range 3.1-19.2]) with diagnoses of brain stem glioma (n = 3), ependymoma (n = 2), anaplastic astrocytoma (n = 1), choroid plexus carcinoma (n = 2), medulloblastoma (n = 1), and primitive neuro-ectodermal tumors (n = 1). Nine were fully evaluable for toxicity. One DLT of fatigue occurred in the 6 evaluable patients enrolled at 1000 mg/m²/dose. No DLTs were experienced by 3 patients treated at 1400 mg/m²/dose. Grade 3 non-DLTs included lymphopenia, neutropenia, and anemia. The median number of courses was 2 (range 1-10). Two patients with a diagnosis of choroid plexus carcinoma and ependymoma continued on therapy for at least 6 months. In the patients treated at 1000 mg/m²/dose, the median (range) MK-0752 Cmax and time to maximum concentration were 85,700 ng/ml (40,600 to 109,000 ng/ml) and 6.1 hour (1-24.1 hours), respectively. CONCLUSIONS: MK-0752 given once weekly is well-tolerated in children with recurrent or refractory CNS malignancies at a dose of 1400 mg/m²/week.