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**Search details**

Cases of brainstem ganglioglioma – management and interventions

**Resources searched**

NHS Evidence; TRIP Database; Cochrane Library; CINAHL; EMBASE; MEDLINE; Google Scholar

**Database search terms:**

brainstem; “brain stem”; brain-stem exp BRAINSTEM; pons; exp PONS; “medulla oblongata”; exp MEDULLA OBLONGATA; midbrain; mid-brain; “mid brain”; exp MESENCEPHALON/; mesencephalon; diencephalon; exp DIENCEPHALON; ganglioglioma*; exp GANGLIOGLIOMA; ganglioma*; ganglioneuroma*; gangliocytoma*

**NHS Evidence search string:**

(“brain stem” OR brainstem OR "mid brain" OR midbrain OR pons OR “medulla oblongata” OR diencephalon OR mesencephalon) (ganglioglioma OR ganglioneuroma OR gangliocytoma OR ganglioglioneuroma OR ganglioma)) OR (“cowden's disease” OR “gorlin syndrome” OR turcot's syndrome)

**Google Scholar search string:**

(“brain stem” OR brainstem OR "mid brain" OR midbrain OR pons OR “medulla oblongata” OR diencephalon OR mesencephalon) (ganglioglioma OR ganglioneuroma OR gangliocytoma OR ganglioglioneuroma OR ganglioma) (~therapy OR ~treatment)

**Summary**

There is a huge amount of research on this subject, especially if I include individual parts of the brain stem – pons, medulla oblongata, mesencephalon, diencephalon and midbrain and the various permutations of ganglioglioma, including gangliocytoma and ganglioneuroma. I have had to limit the search just to instances of ganglioglioma and brainstem. There were several thousand results being returned particularly by EMBASE, so I limited these results to research and case reports published since 1992. I have also included treatment of glioma more generally given that ganglioglioma is a type of glioma.
Guidelines

Children’s Brain Tumour Research Centre
Diagnosis of Brain Tumours in Children Guideline: A Guideline To Assist Healthcare Professionals In The Assessment Of Children Who May Have A Brain Tumour 2010

NICE
Improving outcomes for people with brain and other CNS tumours - the manual 2006

Evidence-based reviews

Clinical Immediate Reference
Brain Tumours in Adults 2011
Brain Tumours in Children 2011

UK Clinical Trials Gateway
Cisplatin and Temozolomide in Treating Young Patients With Malignant Glioma 2006
Combination Chemotherapy With or Without Radiation Therapy in Treating Children With Brain Tumors 2006
Radiation Therapy or Combination Chemotherapy in Treating Patients With Clinically or Radiologically Progressive Low-Grade Gliomas 2006
Carboplatin Plus Vincristine in Treating Children and Adolescents With Low Grade Glioma 1999

Published research

1. Single arc volumetric modulated arc therapy for complex brain gliomas: Is there an advantage as compared to intensity modulated radiotherapy or by adding a partial arc?

Author(s) Davidson M.T.M., Masucci G.L., Follwell M., Blake S.J., Xu W., Moseley D.J., Sanghera P., Wong C.S., Perry J., Tsao M., Sahgal A.

Citation: Technology in Cancer Research and Treatment, June 2012, vol./is. 11/3(211-220), 1533-0346 (June 2012)

Publication Date: June 2012

Abstract: The objective of this study was to determine if volumetric modulated arc therapy (VMAT) offers advantages over intensity modulated radiotherapy (IMRT) for complex brain gliomas and evaluate the role of an additional partial arc. Twelve patients with glioma involving critical organs at risk (OAR) were selected [six low grade brainstem glioma (BG) and six glioblastoma (GB) cases]. BGs were prescribed 54 Gy/30 fractions (frx), and GB treated to 50 Gy/30 frx to a lower dose PTV (PTV50) with a simultaneous integrated boost delivering a total dose of 60 Gy/30 frx to a higher dose PTV (PTV60). VMAT was planned with a single arc (VMAT1) and with an additional coplanar partial arc spanning 90degree (VMAT2). We observed VMAT1 improving the PTV equivalent uniform dose (EUD) for BG cases (p = 0.027), improving the V95 for the PTV50 in GB cases (p = 0.026) and resulting in more conformal GB plans (p = 0.008) as compare to IMRT. However, for the GB PTV60, IMRT achieved favorable V95 over VMAT1 and VMAT2 (0.0046 and 0.008, respectively). The GB total integral dose (ID) was significantly lower with VMAT1 and VMAT2 (p = 0.049 and p = 0.006, respectively). Both VMAT1 and VMAT2 reduced the ID, however, only at the 5 Gy threshold for BG cases (p = 0.011 and 0.005, respectively). VMAT achieved a lower spinal cord maximum dose and EUD for BG cases and higher optic nerve doses, otherwise no significant differences were observed. VMAT1 yielded the fastest treatment times and least MU. We conclude that VMAT offers faster treatment delivery for complex brain tumors while maintaining similar dosimetric qualities to IMRT. Selective dosimetric advantages in terms of spinal cord sparing and lowering the ID are observed favoring the use of an
2. Institutional experience of paediatric high-grade central nervous system tumours: An analysis of 74 patients and review of the literature

Author(s) Pinarli F.G., Oguz A., Karadeniz C., Okur A., Sarac A., Baykaner K., Bora H., Poyraz A.

Citation: Wspolczesna Onkologia, 2012, vol./is. 16/1(26-33), 1428-2526 (2012)

Publication Date: 2012

Abstract: Aim of the study: Although the survival for children with certain central nervous system (CNS) tumour types has improved through current surgical and adjuvant treatment modalities, the prognosis of many high-grade tumours remains poor despite aggressive treatment. The aim of this study is to analyse patients with high-grade brain tumours in our institution to determine the histopathology, clinical characteristics, treatment modalities, and survival. Material and methods: A total of 74 patients with a diagnosis of high-grade brain tumour were analysed. There were a total of 31 patients with embryonal tumours, 27 patients with high-grade glial tumours, 12 patients with brain stem gliomas and 4 patients with other high-grade brain tumours. Results: There were 48 (65%) boys and 26 (35%) girls (ratio: 1.85) with a median age of 99.7 months (range = 2-204 months). The median follow-up period was 19 months (range = 1-204 months). Tumour recurrence was observed in 38 patients (51.4%). The overall survival rate and event-free survival rate of our patients were 27% and 19.5%, respectively. Conclusions: Pediatric high-grade CNS tumours have a very aggressive behaviour and a significant number of children eventually succumb to disease despite multimodal treatment. There is a need of more effective therapeutic approaches for these tumours with poor prognosis. The future improvement in childhood high-grade brain tumour management depends on a better understanding of the molecular genetics and biology of brain tumours.

Source: EMBASE

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3. Incidental brain lesions in children: To treat or not to treat?

Author(s) Bredlau A.-L., Constine L.S., Silberstein H.J., Milano M.T., Korones D.N.

Citation: Journal of Neuro-Oncology, February 2012, vol./is. 106/3(589-594), 0167-594X;1573-7373 (February 2012)

Publication Date: February 2012

Abstract: Central nervous system (CNS) lesions that are discovered incidentally when imaging children for problems that were unrelated to the detected lesion pose a dilemma to physicians. Because there are few data on the outcome of such cases, we retrospectively reviewed the clinical course of a group of children followed at our institution with brain lesions found incidentally on neuroimaging. A database of all children with brain lesions followed at the University of Rochester medical center from 2000 to 2010 was reviewed. Data were obtained regarding presentation, magnetic resonance imaging (MRI) features, treatment, progression-free survival, and overall survival of children with brain lesions found incidentally. Of the 244 children with brain lesions seen over this time period, 21 (8.6%) were found to have incidentally discovered brain lesions. Of these 21 children, 12 (57%) underwent surgical resection of their brain lesions. Ten patients (48%) had symptoms considered to be unassociated with the detected lesion. Lesions were found in the cerebellum (n = 7, 33%), midline (n = 5, 24%), and cerebrum (n = 9, 43%). All lesions were <=5 cm in diameter. Eight patients (38%) had surgery at presentation, one because of imaging features suspicious for a posterior fossae ependymoma, and the seven others because of location in the posterior fossae or brain stem. Of the remaining 13 patients, five had progression of disease on serial MRI scans: four underwent surgery and the fifth was monitored and remained stable after the initial progression stabilized. Nine of the ten patients (90%) with posterior fossae lesions underwent surgery, while only three of 11 with
supratentorial lesions underwent surgery (27%) (P = 0.006). The progression free survival was 94% at 12 months (95% CI 65-99%) and 71% at 24 months (95% CI 39-88%). At a median follow-up of 32 months, the overall survival was 100%. Incidentally detected CNS lesions are usually small. The outcome for children with such lesions is excellent. Close monitoring of these patients with serial MRIs may be a safe alternative to immediate biopsy and/or resection for select patients. 2011 Springer Science+Business Media, LLC.

Source: EMBASE
Available in print at ULHT journal article requests. Complete the online form to obtain articles.

4. Photon and proton therapy planning comparison for malignant glioma based on CT, FDG-PET, DTI-MRI and fiber tracking

Author(s) Rosenschold P.M.A., Engelholm S., Ohlhuess L., Law I., Vogelius I., Engelholm S.A.

Citation: Acta Oncologica, August 2011, vol./is. 50/6(777-783), 0284-186X;1651-226X (August 2011)

Publication Date: August 2011

Abstract: Purpose. The purpose of this study was to compare treatment plans generated using fixed beam Intensity Modulated photon Radiation Therapy (IMRT), inversely optimized arc therapy (RapidArc(R), RA) with spot-scanned Intensity Modulated Proton Therapy (IMPT) for high-grade glioma patients. Plans were compared with respect to target coverage and sparing of organs at risk (OARs), with special attention to the possibility of hippocampus sparing. Method. Fifteen consecutive patients diagnosed with grade III and IV glioma were selected for this study. The target and OARs were delineated based on computed tomography (CT), FDG-positron emission tomography (PET) and T1-, T2-weighted, and Diffusion Tensor Imaging (DTI) magnetic resonance imaging (MRI) and fiber-tracking. In this study, a 6 MV photon beam on a linear accelerator with a multileaf collimator (MLC) with 2.5 mm leaves and a spot-scanning proton therapy machine were used. Two RA fields, using both a coplanar (clinical standard) and a non-coplanar, setup was compared to the IMRT and IMPT techniques. Three and three to four non-coplanar fields where used in the spot-scanned IMPT and IMRT plans, respectively. The same set of planning dose-volume optimizer objective values were used for the four techniques. The highest planning priority was given to the brainstem (maximum 54 Gy) followed by the PTV (prescription 60 Gy); the hippocampi, eyes, inner ears, brain and chiasm were given lower priority. Doses were recorded for the plans to targets and OARs and compared to our clinical standard technique using the Wilcoxon signed rank test. Result. The PTV coverage was significantly more conform for IMPT than the coplanar RA technique, while RA plans tended to be more conform than the IMRT plans, as measured by the standard deviation of the PTV dose. In the cases where the tumor was confined in one cerebral hemisphere (eight patients), the non-coplanar RA and IMPT techniques yielded borderline significantly lower doses to the contralateral hippocampus compared to the standard (22% and 97% average reduction for non-coplanar RA and IMPT, respectively). The IMPT technique allowed for the largest healthy tissue sparing of the techniques in terms of whole brain doses and to the fiber tracts. The maximum doses to the chiasm and brainstem were comparable for all techniques. Conclusion. The IMPT technique produced the most conform plans. For tumors located in the one of the cerebral hemispheres, the non-coplanar RA and the IMPT techniques were able to reduce doses to the contralateral hippocampus. The IMPT technique offered the largest sparing of the brain and fiber tracts. RA techniques tended to produce more conform target doses than IMRT. 2011 Informa Healthcare.

Source: EMBASE
Available in print at ULHT journal article requests. Complete the online form to obtain articles.

5. Neuropathological and neuroradiological spectrum of pediatric malignant gliomas: Correlation with outcome
BACKGROUND: The diagnostic accuracy and reproducibility for glioma histological diagnosis are suboptimal. OBJECTIVE: To characterize radiological and histological features in pediatric malignant gliomas and to determine whether they had an impact on survival. METHODS: We retrospectively reviewed a series of 96 pediatric malignant gliomas. All histological samples were blindly and independently reviewed and classified according to World Health Organization 2007 and Sainte-Anne classifications. Radiological features were reviewed independently. Statistical analyses were performed to investigate the relationship between clinical, radiological, and histological features and survival. RESULTS: Cohort median age was 7.8 years; median follow-up was 4.8 years. Tumors involved cerebral hemispheres or basal ganglia in 82% of cases and brainstem in the remaining 18%. After histopathological review, low-grade gliomas and nonglial tumors were excluded (n = 27). The World Health Organization classification was not able to demonstrate differences between groups and patients survival. The Sainte-Anne classification identified a 3-year survival rate difference between the histological subgroups (oligodendroglioma A, oligodendroglioma B, malignant glioneuronal tumors, and glioblastomas; P = .02). The malignant glioneuronal tumor was the only glioma subtype with specific radiological features. Tumor location was significantly associated with 3-year survival rate (P = .005). Meningeal attachment was the only radiological criteria associated with longer survival (P = .02). CONCLUSION: The Sainte-Anne classification was better able to distinguish pediatric malignant gliomas in terms of survival compared with the World Health Organization classification. In this series, neither of these 2 histological classifications provided a prognostic stratification of the patients. Copyright by the Congress of Neurological Surgeons.

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6. Desmoplastic infantile and non-infantile ganglioglioma. Review of the literature

Author(s) Gelabert-Gonzalez M., Serramito-Garcia R., Arcos-Algaba A.

Citation: Neurosurgical Review, April 2011, vol./is. 34/2(151-158), 0344-5607;1437-2320 (April 2011)

Publication Date: April 2011

Abstract: Desmoplastic gangliogliomas (DIG) are rare primary neoplasms that comprise 0.5-1.0% of all intracranial tumors. Clinically, there are two forms of DIG, the infantile and the non-infantile. These tumors invariably arise in the supratentorial region and commonly involve more than one lobe, preferentially the temporal and frontal. On neuroimaging are seen as large hypodense cystic masses with a solid isodense or slightly hyperdense superficial portion. The histologic diagnosis is characterized by the presence of three different cell lines: astrocytic, neuronal, and primitive neuroectodermal marker sites, which were demonstrable. The treatment of choice is radical surgical excision, and if this is done, achieved complete healing of the patient does not require additional treatment. A literature review of DIG was compiled through Medline/Ovid using the keywords "desmoplastic infantile ganglioglioma", "desmoplastic non-infantile ganglioglioma" covering the years 1984-2009. We present a review of a total of 113 cases of infantile (94) and non-infantile gangliogliomas (19) published to date, examining the clinical, radiologic, surgical, and pathological aspects, as well as the outcome. Desmoplastic gangliogliomas represent a rare tumor group with two well-defined age groups, the children and non-children. Desmoplastic infantile gangliogliomas are the most common and occur in children below 5 years of age, and the large majority of them present within the first year of life. Surgery is the treatment of choice and no complementary treatment is needed in cases of complete tumor resection. Springer-Verlag 2011.

Source: EMBASE
7. A lower-dose, lower-toxicity cisplatin-etoposide regimen for childhood progressive low-grade glioma

**Author(s)** Massimino M., Spreafico F., Riva D., Biassoni V., Poggi G., Solero C., Gandola L., Genitori L., Modena P., Simonetti F., Potepan P., Casanova M., Meazza C., Clerici C.A., Catania S., Sardi I., Giangaspero F.

**Citation:** Journal of Neuro-Oncology, October 2010, vol./is. 100/1(65-71), 0167-594X;1573-7373 (October 2010)

**Publication Date:** October 2010

**Abstract:** After successfully using cisplatin (30 mg/m<sup>2</sup>/day) and etoposide (150 mg/m<sup>2</sup>/day) in ten three-day courses for progressive low-grade gliomas, a subsequent protocol reduced the daily doses of cisplatin (to 25 mg) and etoposide (to 100 mg), with the objective of achieving the same response and three-year PFS rates with lower neurotoxicity and myelotoxicity. We treated 37 patients (median age 6 years); 23 had optochiasmatic tumours and nine were metastatic cases. Diagnoses were clinical in 13 cases and histological in 24, and comprised: pilocytic astrocytoma (17), ganglioglioma (3), pilomyxoid astrocytoma (2), and fibrillary astrocytoma (2). Treatment was prompted by radiological evidence of progression and/or clinical deterioration a median 18 months after the first diagnosis. After initial MRI staging, neurological and clinical examinations were performed before each chemotherapy cycle, with MRI after the first three courses and every three months thereafter. After a median 48 months, a volume reduction was appreciable in 24 cases (65%) and response was maximum 12 months after starting treatment. The three-year EFS and OS rates were 65 and 97%, respectively. Clinical, neurological, or functional improvements were seen in 26/37 cases. No children had a WBC nadir below 2,000/mm<sup>3</sup>. Audiological toxicity caused damage in 4/34 cases. The previous protocol had achieved volume reductions in 70% of cases, causing audiological damage (data updated) in 11/31 (P = 0.023), with three-year PFS and OS rates of 70 and 100%, respectively. Lower doses of cisplatin/etoposide are still effective in progressive low-grade glioma, with less acute and persistent morbidity. 2010 Springer Science+Business Media, LLC.

**Source:** EMBASE

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8. Radiation therapy in paediatric gliomas: Our institutional experience

**Author(s)** Sharma D.N., Goyal S., Muzumder S., Haresh K.P., Bahl A., Julka P.K., Rath G.K.

**Citation:** Neurologia i Neurochirurgia Polska, 2010, vol./is. 44/1(28-34), 0028-3843 (2010)

**Publication Date:** 2010

**Abstract:** Background and purpose: The aim of our retrospective study was to analyze the clinical outcome of paediatric glioma patients treated with radiation therapy (RT) in our institution. Material and methods: We retrieved the case records of all children with gliomas (age < 18 years) who received RT in our department between 2004 and 2007. We analyzed the information regarding patients' demography, clinical details, treatment given, RT details, and survival. The event-free survival (EFS), the period from the date of completion of RT to the date of the event, i.e. death/recurrence, was calculated with respect to age, sex, location of tumour (brainstem vs. non-brainstem), histopathology (low grade vs. high grade), extent of surgical resection, dose and duration of RT, and use of chemotherapy. Results: A total of 70 children with glioma received RT during the above-mentioned period. The 3-year EFS rate for all patients was 44% and the median EFS period was 18 months. The 3-year EFS in patients who underwent surgical decompression and no surgery was 58% and 25%, respectively (p < 0.05). Patients with brainstem lesions...
had statistically significantly lower 3-year EFS to non-brainstem gliomas (28% vs. 56%, p < 0.01). Chemotherapy use showed no statistically significant trend towards better survival. Conclusions: RT is an effective modality of treatment in paediatric glioma patients in our setup. Early use of RT in incompletely resected low-grade gliomas is worth revisiting. Results of chemotherapy in high-grade glioma and brainstem gliomas are encouraging.

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9. Endocrinologic assessment in patients with diffuse intrinsic pontine glioma (DIPG)

Author(s) Zimmerman M., Marcus K.J., Cohen L.E., Chordas C., Chi S.N., Lee M., Manley P.E., Robison N., Ullrich N.J., Goumnerova L., Kieran M.W.

Citation: Neuro-Oncology, June 2010, vol./is. 12/6(ii123), 1522-8517 (June 2010)

Publication Date: June 2010

Abstract: PURPOSE: Diffuse intrinsic pontine glioma (DIPG) is a highly aggressive pediatric malignancy that cannot be cured with currently available therapy. Though radiation therapy frequently results in disease stabilization, the majority of patients experience progression and rapidly succumb to disease. Since dose to the hypothalamus and pituitary regions can be considerable, we performed a retrospective chart review of patients seen at the DFCI/CHB for DIPG to assess the dose of radiation to the hypothalamus and pituitary and frequency of endocrinological evaluation. PATIENTS AND METHODS: Between 1994 and 2009, 108 patients were evaluated for the diagnosis of DIPG. Patients receiving focal radiotherapy whose radiation summaries were available and who had clinical follow-up at DFCI/CHB were included for review. Data was extracted after approval from the IRB. RESULTS: A review of the radiation fields demonstrated that over 90% of patients received a minimum dose of 3000 cGy of radiation to the hypothalamus and pituitary. Many patients reported symptoms such as fatigue and constipation towards the end of life. The minority of patients, however, underwent endocrinologic evaluation, despite a median time to death of 15 months (range 3-59 months) CONCLUSIONS: Screening for endocrine function is done infrequently despite the significant dose of radiation delivered to the hypothalamus/pituitary in patients with DIPG. Greater attention to endocrine status, despite the terminal nature of this disease, might enhance symptom management towards the end of life and improve quality of life for these patients.

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10. Long-term follow-up of children treated for low grade glioma

Author(s) Ater J.L., Xu A., Cruz S.C., Mahajan A., Weinberg J.S.

Citation: Neuro-Oncology, June 2010, vol./is. 12/6(ii98), 1522-8517 (June 2010)

Publication Date: June 2010

Abstract: PURPOSE: The purpose of this study was to determine the long-term survival, rate and types of secondary tumors, and medical outcomes of children diagnosed with low grade glioma. METHODS: A retrospective chart review was performed identifying subjects from our Children's Cancer Hospital database diagnosed with low grade glioma (LGG) between 1970 and 2006, at age less than 18 years, and having follow-up information available. RESULTS: There were 199 subjects identified, 55% boys, ranging in age from 1 month to 18 yrs. (median 5 yrs.) at diagnosis and 30.7 % had neurofibromatosis type 1 (NF1). Period of follow-up ranged from 0.6 to 39 years with age at last follow-up 4 to 54 years. Tumors were located in cerebellum: 30 (15.2%); hypothalamic/optic pathway 111 (56.1%); brainstem 25 (12.6%); and cerebral hemisphere/thalamus 28 (14.1%). Tumor types were 52% pilocytic astrocytoma, 27% optic pathway without biopsy, and 21% other
LGG. Treatments included various combinations of surgery, chemotherapy, and radiation. Many had multiple treatments. The survival rates at 5, 10, and 15 years were: 93%, 81%, and 74% respectively. Two patients had malignant transformation and 5 had malignant tumor at another area of the brain from the original. Details of second malignancies will be presented. Late occurring morbidity included overweight/obesity 58%, visual deficits 17%, need for hormonal replacement 28%. CONCLUSIONS: Long-term survival into adulthood is possible for children with low grade glioma, even after recurrence. However, morbidity and risk of recurrence continues throughout life. Occurrence of malignant transformation or second malignancy is low.

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11. Treatment concepts for pediatric low-grade gliomas in critical locations
Author(s) Peraud A., Tonn J.C., Kreth F.W.
Citation: Neuro-Oncology, June 2010, vol./is. 12/6(iii8), 1522-8517 (June 2010)
Publication Date: June 2010
Abstract: OBJECTIVE: In search for optimized treatment conditions for children with WHO grade I and II gliomas not accessible to complete resection, brachytherapy (BT) has been proven to be beneficial. BT with temporary Iodine-125-seeds provides precise radiosurgical planning sparing surrounding normal tissue. The results in 29 pediatric cases treated with BT after partial tumour resection or with BT alone, are presented. METHODS: 15 boys and 14 girls were included in the present study. Mean age at the time of BT was 9 years. Tumour location was hypothalamic-suprasellar in 9, lobar in 8, deep in 6, within the brainstem in 4, and in the cerebellum in 2 children. Histology revealed 18 pilocytic astrocytomas, 9 fibrillary astrocytomas, one ependymoma and one ganglioglioma. Partial resection with subsequent BT was performed in 12 cases, 17 tumours were stereotactically biopsied and implanted with Iodine-125-seeds. RESULTS: Mean follow-up time was 33 months. Ten tumours showed complete regression 6 to 40 months after seed implantation, tumours decreased in size in 18 children 2 to 16 months after BT. Two children developed space occupying radionecrosis which had then to be resected leading to neurological improvement. One boy died due to tumour progression of his WHO grade II astrocytoma. Twelve children even experienced an improvement of their previous neurological deficits. CONCLUSIONS: Brachytherapy is a safe and effective method even in the younger patient group under 3 years of age. Microsurgery in combination with BT or BT as single treatment provides excellent surgical outcome, good tumour control and low morbidity.

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12. Comparisons of radiographic and clinical definitions of disease progression in pediatric patients with newly diagnosed intrinsic diffuse Brainstem Gliomas (BSG) Treated on a PBTC Phase II trial of Tipifarnib and Radiation
Author(s) Haas-Kogan D., Anwar M., Kocak M., Rodriguez D., Prados M.D., Banerjee A., Blaney S.M., Boyett J.M., Kun L.E., Poussaint T.Y.
Citation: International Journal of Radiation Oncology Biology Physics, November 2010, vol./is. 78/3 SUPPL. 1(S151-S152), 0360-3016 (01 Nov 2010)
Publication Date: November 2010
Abstract: Purpose/Objective(s): Current methods for assessing the response to therapy of
Glial tumors have limitations and therefore controversy exists regarding the best definition of tumor response or progression. Establishing uniform criteria is critical since clinical trials rely on these to assess efficacy of standard treatments and novel agents. In this study we sought to compare bi-dimensional and volumetric MR measurements, as well as clinical assessments as definitions of disease progression after radiation therapy in pediatric patients with BSG treated on a Pediatric Brain Tumors Consortium (PBTC) Phase II trial of tipifarnib and radiation (RT). Materials/Methods: PBTC has completed a phase II study of tipifarnib, a farnesyltransferase inhibitor, administered concurrently with RT in children with newly diagnosed BSGs. For the 37 patients who had 2 or more MRI measurements on treatment, all MRIs were centrally reviewed by the PBTC Neuro-Imaging Center with bi-dimensional and volumetric measurements obtained retrospectively. Results: In assessing “pseudo-progression” we asked how many patients met the 25% threshold for progressive disease on the first post-radiation scan, done 2 weeks after completion of radiation. For 3 patients, this MRI showed progressive disease and in all 3 of these patients disease continued to progress, resulting in death soon thereafter. For 14 of 37 patients, bi-dimensional and volumetric measurements documented progressive disease at the same time point. Four patients progressed by volumetric measurements but never progressed by bi-dimensional measurements; while in only 1 patient disease progressed by bi-dimensional measurements without progression by volumetric measurements. In 4 cases disease progression was seen by bi-dimensional measurements earlier than by volumetric measurements, while in 6 cases tumor volume indicated progressive disease earlier than tumor area. Eighteen patients remained on study and continued to receive study drug despite meeting the 25% threshold for progressive disease either by tumor volume or area. However, no differences in progression free survival were evident regardless of whether progressive disease was defined by tumor volume, tumor area, or institutional decisions. Conclusions: Among 37 newly diagnosed children with BSG treated with a farnesyltransferase and concurrent radiation no "pseudo-progression" was seen. Regardless of whether progressive disease was defined by tumor volume, tumor area, or evaluations by the treating sites no differences in progression free survival were evident.

Source: EMBASE

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13. Bevacizumab as therapy for radiation necrosis in four children with pontine gliomas

Author(s) Liu A.K., Macy M.E., Foreman N.K.

Citation: International journal of radiation oncology, biology, physics, November 2009, vol./is. 75/4(1148-1154), 1879-355X (15 Nov 2009)

Publication Date: November 2009

Abstract: PURPOSE: Diffuse pontine gliomas are a pediatric brain tumor that is fatal in nearly all patients. Given the poor prognosis for patients with this tumor, their quality of life is very important. Radiation therapy provides some palliation, but can result in radiation necrosis and associated neurologic decline. The typical treatment for this necrosis is steroid therapy. Although the steroids are effective, they have numerous side effects that can often significantly compromise quality of life. Bevacizumab, an antibody against vascular endothelial growth factor, has been suggested as a treatment for radiation necrosis. We report on our initial experience with bevacizumab therapy for radiation necrosis in pediatric pontine gliomas. MATERIALS AND METHODS: Four children with pontine gliomas treated at the Children's Hospital in Denver and the University of Colorado Denver developed evidence of radiation necrosis both clinically and on imaging. Those 4 children then received bevacizumab as a treatment for the radiation necrosis. We reviewed the clinical outcome and imaging findings. RESULTS: After bevacizumab therapy, 3 children had significant clinical improvement and were able to discontinue steroid use. One child continued to decline, and, in retrospect, had disease progression, not radiation necrosis. In all cases, bevacizumab was well tolerated. CONCLUSIONS: In children with pontine gliomas, bevacizumab may provide both therapeutic benefit and diagnostic information. More formal evaluation of bevacizumab in these children is needed.

Source: EMBASE
14. Ganglioglioma in the cerebellopontine angle of an adult without seizures
Author(s) Cuthikonda B., Buckleair L.J., Goodman J.C., Powell S.Z., Rose J.E.
Citation: The Journal of the Louisiana State Medical Society : official organ of the Louisiana State Medical Society, May 2009, vol./is. 161/3(143-146), 0024-6921 (2009 May-Jun)
Publication Date: May 2009
Abstract: We present a rare case of an adult patient without seizures who is found to have a ganglioglioma occurring in the cerebellopontine angle. A 52-year-old woman with ataxia, headaches, and falling episodes underwent neuroimaging. Magnetic resonance imaging (MRI) revealed a smooth, somewhat lobulated mass in the left cerebellopontine angle. The mass was hypointense on T1-weighted imaging, hyperintense on T2-weighted imaging, and did not enhance after administration of gadolinium. Left retromastoid craniectomy was performed, and the mass was noted to be exophytic from the brain stem. The exophytic component was resected. Light microscopic findings were consistent with ganglioglioma. This was confirmed with immunohistochemical studies. Ganglioglioma is a rare tumor of the central nervous system that typically presents with seizures in children and young adults. Occurrence of this tumor in the cerebellopontine angle is extremely unusual; this rarity is magnified by its occurrence in an adult patient without a history of seizures. Our case illustrates that ganglioglioma should be considered in the differential diagnosis of cerebellopontine angle masses at any age. This appears to be especially true when dealing with masses that are non-enhancing on imaging.
Source: EMBASE
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15. Interferon-beta, MCNU, and conventional radiotherapy for pediatric patients with brainstem glioma
Author(s) Ohno M., Natsume A., Fujii M., Ito M., Wakabayashi T.
Citation: Pediatric blood & cancer, July 2009, vol./is. 53/1(37-41), 1545-5017 (Jul 2009)
Publication Date: July 2009
Abstract: BACKGROUND: Most children with brainstem glioma die within 2 years of diagnosis, and the median survival time for patients with this condition is less than 1 year. The role of chemotherapy in the treatment of children with brainstem glioma is not well defined. The primary aim of this study is to evaluate the effects of treatment with interferon-beta (IFN-beta), ranimustine (MCNU), and radiotherapy (IMR therapy) administered to brainstem glioma patients treated at our institution. We also determined patient response to IMR therapy by evaluating O(6)-methylguanine-DNA methyltransferase (MGMT) promoter methylation in serum DNA. PROCEDURES: We retrospectively reviewed 15 patients who were newly diagnosed to have brainstem tumors and were administered IFN-beta (1-2 MIU/day, days 1-7; 0.5-1 MIU/day, days 8-14) and MCNU (80 mg/m(2) on day 2) concurrently with conventional radiotherapy. Responses were assessed by MRI scan, and data on clinical course and toxicity were obtained from the medical records. The MGMT promoter methylation status in serum DNA of five patients was assayed by methylation-specific PCR. RESULTS: Of the 15 patients, partial response, stable disease, and progressive disease were noted in 5 patients each. The median overall survival time and the median progression-free survival time were 14.7 and 4.6 months, respectively. The protocol was not terminated in any of the patients because of hematological toxicity, nephrotoxicity, or neurotoxicity. The MGMT promoter methylation status in the serum appeared to correlate with a positive response to IMR therapy. CONCLUSIONS: The IMR combination therapy is well tolerated and may be a promising treatment for brainstem glioma. Copyright 2009 Wiley-Liss, Inc.
Source: EMBASE
Available in print at ULHT journal article requests. Complete the online form to obtain articles.

**Author(s)** Frazier J.L., Lee J., Thomale U.W., Noggle J.C., Cohen K.J., Jallo G.I.

**Citation:** Journal of neurosurgery. Pediatrics, April 2009, vol./is. 3/4(259-269), 1933-0707 (Apr 2009)

**Publication Date:** April 2009

**Abstract:** Diffuse intrinsic pontine gliomas constitute ~ 60-75% of tumors found within the pediatric brainstem. These malignant lesions present with rapidly progressive symptoms such as cranial nerve, long tract, or cerebellar dysfunctions. Magnetic resonance imaging is usually sufficient to establish the diagnosis and obviates the need for surgical biopsy in most cases. The prognosis of the disease is dismal, and the median survival is < 12 months. Resection is not a viable option. Standard therapy involves radiotherapy, which produces transient neurological improvement with a progression-free survival benefit, but provides no improvement in overall survival. Clinical trials have been conducted to assess the efficacy of chemotherapeutic and biological agents in the treatment of diffuse pontine gliomas. In this review, the authors discuss recent studies in which systemic therapy was administered prior to, concomitantly with, or after radiotherapy. For future perspective, the discussion includes a rationale for stereotactic biopsies as well as possible therapeutic options of local chemotherapy in these lesions.

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17. Outcome and prognostic features in pediatric gliomas: A review of 6212 cases from the surveillance, epidemiology, and end results database

**Author(s)** Qaddoumi I., Sultan I., Gajjar A.

**Citation:** Cancer, December 2009, vol./is. 115/24(5761-5770), 0008-543X;1097-0142 (15 Dec 2009)

**Publication Date:** December 2009

**Abstract:** BACKGROUND: Pediatric gliomas are rare and heterogeneous tumors. The Surveillance, Epidemiology, and End Results (SEER) database allows a large-scale analysis of the clinical characteristics and prognostic features of these tumors. METHODS: The authors analyzed available SEER data on 6212 patients younger than 20 years at diagnosis of glioma (1973-2005), according to 4 age categories: <1 year, 1-3 years, 3-5 years, and 5-20 years. RESULTS: The overall 5- and 10-year survival estimates were 71%+/-.0.62% (standard error) and 68%+/-.0.67%, respectively. Forty-one percent of gliomas were cerebral; the frequency of cerebellar tumors (22%-32% of gliomas) increased sharply after the first year of life. Of the tumors for which grade was available, 77% were low grade (grade I or II). Tumor grade emerged as the most significant independent prognostic factor in all age groups except the youngest age group, in which extent of resection was most significant. Surgery other than gross total resection was an adverse prognostic factor (hazard ratio, 2.18; 95% confidence interval, 1.78-2.67). Age <3 years predicted a greater likelihood of survival in patients with high-grade gliomas and brainstem tumors. Conversely, age <3 years predicted a lower likelihood of survival in patients with low-grade gliomas. Children aged <1 year received less radiotherapy than older patients (P < .0001) and were less likely to undergo gross total resection (P < .0001). CONCLUSIONS: The survival of children with gliomas is influenced by histologic subtype, age, and extent of resection. Despite its limitations, the SEER database provides a useful tool for studies of rare tumors such as pediatric gliomas. 2009 American Cancer Society.

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18. Adult cerebellopontine angle medulloblastoma originating in the pons mimicking focal brainstem tumor

**Author(s)** Yoshimura J., Nishiyama K., Fukuda M., Watanabe M., Igarashi H., Fujii Y.

**Citation:** Journal of Neuroimaging, October 2009, vol./is. 19/4(385-387), 1051-2284;1551-6569 (October 2009)

**Publication Date:** October 2009

**Abstract:** We herein report a rare case of cerebellopontine angle (CPA) medulloblastoma originating in the brainstem that demonstrated a very unusual clinical presentation and radiological appearances. A 25-year-old female was admitted to our hospital with a right hearing disturbance and a right facial palsy. A small non-enhanced lesion having minimal mass effect in the right CPA was identified by using a 1.5-tesla-MR system, whose size remained almost unchanged a year. The 3-tesla MR images revealed that the precise region was in the right side of the tegmentum of the lower pons to the inferior cerebellar peduncle and the flocculus. MR spectroscopic images using a 3-tesla system revealed a high ratio of choline-to-N-acetylaspartate in the region of interest in comparison to the contra-lateral side. Craniotomy and biopsy were performed. The histopathological diagnosis was medulloblastoma. The patient received craniospinal irradiation and chemotherapy, and achieved complete remission by the time of the follow-up MR images. She is now doing well with a full recovery of the right facial palsy. MR spectroscopic imaging is considered to be quite useful for the management of this rare type of brainstem tumor. 2009 by the American Society of Neuroimaging.

**Source:** EMBASE

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Available in print at ULHT journal article requests. Complete the online form to obtain articles.


**Author(s)** Frazier J.L., Lee J., Thomale U.W., Noggle J.C., Cohen K.J., Jallo G.I.

**Citation:** Journal of Neurosurgery: Pediatrics, April 2009, vol./is. 3/4(259-269), 1933-0707;1933-0715 (April 2009)

**Publication Date:** April 2009

**Abstract:** Diffuse intrinsic pontine gliomas constitute ~ 60-75% of tumors found within the pediatric brainstem. These malignant lesions present with rapidly progressive symptoms such as cranial nerve, long tract, or cerebellar dysfunctions. Magnetic resonance imaging is usually sufficient to establish the diagnosis and obviates the need for surgical biopsy in most cases. The prognosis of the disease is dismal, and the median survival is < 12 months. Resection is not a viable option. Standard therapy involves radiotherapy, which produces transient neurological improvement with a progression-free survival benefit, but provides no improvement in overall survival. Clinical trials have been conducted to assess the efficacy of chemotherapeutic and biological agents in the treatment of diffuse pontine gliomas. In this review, the authors discuss recent studies in which systemic therapy was administered prior to, concomitantly with, or after radiotherapy. For future perspective, the discussion includes a rationale for stereotactic biopsies as well as possible therapeutic options of local chemotherapy in these lesions.

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20. Endoscopic options in children: Experience with 134 procedures: Clinical article

**Author(s)** Oertel J.M.K., Baldauf J., Schroeder H.W.S., Gaab M.R.

**Citation:** Journal of Neurosurgery: Pediatrics, February 2009, vol./is. 3/2(81-89), 1933-0707;1933-0715 (February 2009)
Abstract: Object. There are frequent applications for endoscopy in neurosurgery. However, endoscopic surgery in children has peculiar characteristics and is associated with different rates of success. In this study, the authors report on their experience with 134 consecutive endoscopy procedures performed in 126 patients < 18 years of age. Methods. Between April 1993 and October 2007, 134 endoscopic procedures were performed in 126 children. Indications for surgery included brain tumors in 48 children, cystic lesions in 24, aqueductal stenosis in 23, various malformations in 20, hemorrhage and infarction in 6, and isolated ventricles in 5 children. In this long-term follow-up study, data were analyzed with respect to clinical and radiological success rates, as well as shunt dependence both in relation to lesion origin, and to the type of endoscopic procedure performed (endoscopic third ventriculostomy [ETV], septostomy, aqueductoplasty, or cystocisternostomy). Finally, the influence of patient age on the success rate was evaluated. Results. In 114 patients, restoration of CSF circulation was the goal of endoscopy, but in 2 patients only ventriculoscopy was performed followed by ventriculoperitoneal shunt placement. In 12 of 114 patients, tumor biopsy sampling or resection was performed simultaneously with shunt placement. In another 12 patients, only endoscopic tumor resection without CSF circulation restoration was done. The follow-up period ranged from 1 to 6 years. Thirteen tumor biopsies, 7 partial tumor resections, and 4 endoscopically complete tumor resections were performed. An intraoperative switch to microsurgery was made in 2 patients because of recurrent hemorrhage and an overly time-consuming endoscopic surgery. Cerebrospinal fluid circulation was successfully restored in 81 (72%) of 112 patients, with the use of endoscopy in the setting of tumor-related hydrocephalus providing the best results (86% success rate). However, of the various endoscopic procedures, cyst openings (cystocisternostomy, cystoventriculostomy, and ventriculocystocisternostomy) provided the best results—superior even to ETV with a success rate of 77% and no complications. In contrast, endoscopic aqueductoplasty had a high failure and complication rate. Patients < 6 months old who underwent ETV, septostomy, or aqueductoplasty had poor results and became more frequently shunt dependent than older children. Conclusions. Overall, endoscopy can be considered safe and effective in children. Based on the authors’ data, acute hydrocephalus cases such as those caused by tumors are the best candidates for endoscopic CSF flow restoration. Interestingly, cyst openings to the ventricles or cisterns were the most successful endoscopic techniques with the lowest complication rate. Aqueductoplasty should be reserved for selected cases. Finally, the success rate of endoscopic techniques remains poor in infants < 6 months of age; this was not only true of ETV, but also other techniques such as septostomy and aqueductoplasty.

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21. Paediatric high and low grade glioma: The impact of tumour biology on current and future therapy

Author(s) Hargrave D.

Citation: British Journal of Neurosurgery, August 2009, vol./is. 23/4(351-363), 0268-8697;1360-046X (August 2009)

Publication Date: August 2009

Abstract: Gliomas are the most common type of paediatric brain tumour and range from benign low grade gliomas which can be resected/observed to aggressive brainstem gliomas with dismal survival rates. Current therapies rely on neurosurgery, radiotherapy, chemotherapy or combination of these conventional modalities and although histopathology helps to direct therapy, molecular pathology has so far not played a major role in the management of paediatric glioma. However, increasing knowledge of glioma biology is starting to impact on drug development towards targeted therapies. Pilocytic astrocytoma, the most common childhood low grade brain tumour, has recently been shown to harbour an activated BRAF/MAPK/ERK pathway in the majority of cases; this represents an attractive target for new agents. The molecular biology of adult malignant glioma is now well described and targeted therapies against VEGFR are already playing a role in the management of glioblastoma. It is likely that high grade gliomas in children and adults share common aberrant molecular pathways but the frequency and mechanisms involved
probably will exhibit key differences and on-going comprehensive molecular analyses of paediatric high grade glioma are essential to determine which targets are important in children. However, selection for specific targeted therapy is unlikely to be based on, or restricted by, age but will require individual case by case testing for target presence in order to direct and maximise the efficacy of molecular therapy. Brainstem glioma remains a tumour with a dismal prognosis but relatively little is known about the underlying biology and progress will require a concerted effort to collect tissue by biopsy and autopsy to allow appropriate analysis to identify and validate targets. A new era of molecular based therapies offers the promise of major benefits in the management of paediatric glioma but translating this promise into reality will require further understanding of the biology driving these tumours. The Neurosurgical Foundation.

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22. Surgical considerations for 'intrinsic' brainstem gliomas: Proposal of a modification in classification

Author(s) Mehta V., Chandra P., Singh P., Garg A., Rath G.
Citation: Neurology India, July 2009, vol./is. 57/3(274-281), 0028-3886;1998-4022 (01 Jul 2009)
Publication Date: July 2009
Abstract: Background: Brainstem gliomas are highly heterogeneous tumors both in their clinical manifestation and in their pathology. Despite significant advances in the surgery for brainstem gliomas many aspects of this pathology are still unclear Objective: To evaluate the clinical, radiological and surgical outcome of 40 focal 'intrinsic' brainstem gliomas and propose a surgical strategy-oriented classification. Materials and Methods: A total of 40 focal 'intrinsic' ("expanding variety") tumors have been operated over a period of 8.5-years (January 1998-June 2007). Our criteria included patients with (1) well-defined gadolinium enhancing tumor; (2) relatively long duration of symptoms (> six months) and (3) good neurological functional status and independent for all activities of daily living. The cutoff size of 2 cm was not rigidly adhered to. Results: The 'intrinsic' brainstem tumors were classified into three types: Expanding, diffuse infiltrative and pure ventral varieties. Only patients with expanding variety of brainstem gliomas were subjected to surgery, mean age 19.2 years (range 4-55 years) and male to female ration mean: 3:2). The tumor location included pons (n=19), midbrain (n=13) and medulla (n=8). Surgical approaches included midline suboccipital (n=28), retromastoid (n=7), subtemporal (n=3) and supracerebellar-infratentorial (n=2). Thirty-two cases with 'diffuse infiltrative' and 'pure ventral' variety were given radiotherapy only. Histology pathology revealed pilocytic variety (n=10), Grade II (n=17) and Grade III (n=13). There was one death in the surgical series (due to aspiration). Complications included meningitis (n=2), wound infection (n=1), chest infection (n=5) and transient mutism (n=1). Follow-up ranged from 3-68 months. Overall, 36 improved /remained same and three worsened in their clinical status at the time of discharge. Conclusion: The surgical management of intrinsic brainstem tumors presents a surgical challenge; radical excision yielded a good outcome in the majority of cases. The authors propose a classification system for 'intrinsic' brainstem tumors for defining surgical strategy.

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23. Brainstem gliomas- Retrospective analysis of 86 patients

Author(s) Ueoka D.I., Nogueira J., Campos J.C., Filho P.M., Ferman S., Lima M.A.
Citation: Journal of the Neurological Sciences, June 2009, vol./is. 281/1-2(20-23), 0022-
Abstract: Brainstem gliomas constitute 10% of brain tumors in children and less than 2% in adults. Since therapeutic options are limited and brainstem gliomas are associated with a high morbidity and mortality, we sought to analyze the prognostic factors associated with a better outcome. We reviewed the records of 86 patients with brainstem gliomas treated between 1996 and 2006. We recorded demographic and clinical variables as well as radiological findings and survival. Patients were divided in two groups regarding overall survival: late progressors (survival >= 12 months) or early progressors (survival< 12 months). Of 86 patients with brainstem gliomas, 55.8% were females. The mean age at diagnosis was 14.2 years (range 1 to 52 years). Twenty-four (27.9%) patients were adults. Lesions were located at pons in 75.6% of patients, midbrain in 15.1% and medulla in 9.3%. There was no difference between early and late progressors concerning gender, age at onset, location at pons, presence of necrosis or contrast enhancement observed at MRI or surgical resection. In both univariate and multivariate analysis, only a short duration of symptoms before diagnosis (< 3 months) was associated with a worst prognosis (odds ratio 5.59, 95% CI 1.94 to 16, p = 0.0014). A short duration of symptoms, which may imply a more aggressive tumor, was associated with a worst prognosis in patients with brainstem gliomas. This information may be useful in the selection of patients for future therapeutic trials. 2009 Elsevier B.V. All rights reserved.

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24. Over a 10-year survival and complete response of a patient with diffuse intrinsic brainstem glioma (DBSG) treated with antineoplastons (ANP)

Author(s) Weaver R.A., Szymkowski B., Burzynski S.R.

Citation: Neuro-Oncology, December 2009, vol./is. 11/6(923), 1522-8517 (December 2009)

Publication Date: December 2009

Abstract: Our purpose is to report a case of a long-term complete response (CR) in a DBSG treated at our center and to discuss the factors contributing to the success. The patient received intravenous injections of ANP every 4 h through a subclavian central venous catheter via a double channel infusion pump followed by PO ANP only. Response was assessed by gadolinium-enhanced MRIs of the brain. The patient is currently a 10.5-year-old Caucasian female who, as a 6-week-old infant, was diagnosed with a DBSG on August 12, 1998. The tumor was inoperable and the pediatric oncology service felt that chemotherapy as well as radiation therapy would not be an option considering the potential toxicity and the age of the patient. On October 14, 1998, she began IV ANP under the FDA’s special exception to phase II protocol BC-BT-11, was converted to PO ANP on June 8, 2000, and permanently discontinued ANP on July 8, 2004. She achieved CR in late February 1999 after discontinuation of dexamethasone and MRI of the brain showed resolution of the enhancing tumor. She developed only one episode of grade 3 vomiting, which resolved within 3 days. Her most recent MRI of the brain on April 2, 2008, did not show any sign of recurrence. In November 2008, her father stated that clinically she was doing very well. ANP is a multigene-targeted therapy that is well tolerated with minimal and reversible adverse events and has multiple different mechanisms of action by affecting the AKT, RAS, TP53, p21, and PTEN pathways. This patient with DSBG achieved CR and over a 10-year survival after treatment with ANP. These promising results have already been confirmed in a larger group of children in phase II studies.

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25. Nimotuzumab and radiotherapy in children and adolescents with brain stem glioma: Preliminary results from a Phase II study

**Author(s)** Crombet T., Cabanas R., Alert J., Valdes J., Gonzalez M.C., Pedrayes J.L., Rios M., Leyva T., Herrera R., Avila M.

**Citation:** European Journal of Cancer, Supplement, September 2009, vol./is. 7/2-3(497), 1359-6349 (September 2009)

**Publication Date:** September 2009

**Abstract:** Background: Several EGFR-targeting products have been approved worldwide for the treatment of different tumor localizations. Nimotuzumab is a humanized, anti-EGFR monoclonal antibody registered in several countries for the treatment of advanced head and neck cancer and recurrent glioma. A Phase II, open label clinical trial was designed to evaluate the progression-free survival rate at 6 months, as well as the overall survival, of children and adolescents newly diagnosed with brain stem gliomas treated with nimotuzumab in combination with external beam radiotherapy

**Material and Methods:** Newly diagnosed patients with clinical and radiological evidence of brain stem tumor, aged between 3-18 years, Karnofsky >40, adequate renal, liver and hematological functions, were eligible. Nimotuzumab was administered at a dose of 150 mg/m² weekly for 12 weeks concomitantly with external beam radiotherapy (induction therapy). Treatment consolidation consisted of similar doses of nimotuzumab at a 2-week interval except in cases of significant deterioration of the performance status. Tumor evaluation was performed using MRI every 12 weeks. Results: Ten patients have been enrolled in this study to date. After completing induction therapy, 8 patients were evaluable for response, 7 patients achieved stable disease (SD), while 1 patient progressed. After 24 weeks, 6 patients were evaluable and all of them showed at least disease stabilization. At the 48 week evaluation there were 3 evaluable patients and 2 of them had partial responses. The most frequent adverse event was grade 1-2 mucositis. None of the patients developed skin rash. The study is ongoing and updated results will be presented. Conclusions: Nimotuzumab is safe. Preliminary results suggest efficacy of the humanized anti-EGFR MAβ in combination with radiotherapy in children and adolescents newly diagnosed with brain stem glioma. Trial continuation is warranted.

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26. Management of diffuse glioma in children: A retrospective study of 27 cases and review of literature

**Author(s)** Piette C., Deprez M., Born J., Michotte A., Munaut C., Closon M.-T., Rutten I., Dresse M.-F., Forget P., Schmitz V., Misson J.-P., Hoyoux C.

**Citation:** Acta Neurologica Belgica, June 2008, vol./is. 108/2(35-43), 0300-9009 (June 2008)

**Publication Date:** June 2008

**Abstract:** Gliomas are the most common CNS tumours in children and present either as circumscribed tumours or diffusely infiltrative neoplasms. Diffuse gliomas develop both in the cerebral hemispheres and the brainstem and have a poor prognosis. Guidelines for the therapy of these tumours are still debated. In this study, we reviewed the clinical features of 27 consecutive patients with diffuse gliomas admitted to the Department of Paediatrics of CHR Citadel, University of Liege, between 1985 and 2005. We review their clinical presentation, diagnosis, treatment and outcome with reference to the published literature.

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27. Brainstem lesions presenting with nausea and vomiting
Author(s) Rosemergy I., Mossman S.

Citation: The New Zealand medical journal, 2007, vol./is. 120/1254(U2532), 1175-8716 (2007)

Publication Date: 2007

Abstract: Positional vomiting is an important alerting sign for the presence of a brainstem central nervous system (CNS) lesion. Failure to identify another cause of protracted vomiting should prompt consideration of a CNS cause.

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28. A fourth ventricular ganglioneurocytoma representing with cerebellar epilepsy: A case report and review of the literature

Author(s) Dagcinar A., Hilmi Kaya A., Ali Tasdemir H., Kuruoglu E., Sabancilar Z., Sav A.

Citation: European Journal of Paediatric Neurology, September 2007, vol./is. 11/5(257-260), 1090-3798;1532-2130 (September 2007)

Publication Date: September 2007

Abstract: Fourth ventricular low-grade tumoral or dysplastic neuronal lesions have been reported as an epileptic focus for recently described cerebellar epilepsy in the form of repetitive and stereotyped attacks of hemifascial spasm, eye blinking, fascial movements, head deviation and dysautonomic manifestations. The case of a 3-month old infant having fourth ventricular mass with similar symptoms such as paroxysmal facial movements, eye blinking, eyelid contractions and abnormal head posture is reported in this article. After a few days of her admission, her attacks displayed a new form with altered consciousness and left limb jerks which were unresponsive to medical therapy. Following the surgical excision of the lesion 10 months ago, attacks disappeared and she is still seizure free. Histopathological diagnosis was ganglioneurocytoma. The seizures (which may be intractable in cerebellar epilepsy) are thought to have arisen from subcortical structures such as cerebellum, brain stem nuclei or the lesion itself. In the case of intractable episodes, surgical excision may prevent further seizures and help patients have a normal cognitive and motor development. 2007 European Paediatric Neurology Society.

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29. Interstitial iodine-125 radiosurgery alone or in combination with microsurgery for pediatric patients with eloquently located low-grade glioma: A pilot study

Author(s) Peraud A., Goetz C., Siefert A., Tonn J.C., Kreth F.W.

Citation: Child’s Nervous System, January 2007, vol./is. 23/1(39-46), 0256-7040 (January 2007)

Publication Date: January 2007

Abstract: Purpose: The optimal therapeutic management of children with World Health Organization grade I and II gliomas not accessible to complete resection is poorly defined. Radical surgical resection is the first-line treatment for large hemispheric tumors, whereas interstitial iodine-125 radiosurgery (IRS) might be an attractive treatment concept for selected patients with small (tumor diameter in the range of 4 cm) and circumscribed tumors in any location of the brain. Precise high-dose application, maximal sparing of surrounding normal tissue, and the absence of long-term complications have been reported to be the hallmark of IRS. Therefore, the therapeutic impact and the risk of IRS alone or in combination with microsurgery (in case of larger tumor volumes) were prospectively examined. Methods: Seven boys and four girls were included (mean age, 6.8 years; range, 11 months to 16 years). IRS (after stereotactic biopsy) was considered to be indicated for circumscribed tumors with a diameter in the range of 4 cm (four cases). For larger tumors,
a combined microsurgical/radiosurgical approach was preferred (seven patients). Temporary iodine-125 seeds were used exclusively (tumor dose calculated to the boundary, 54 Gy; dose rate, 10 cGy/h). Tumor location was hypothalamic/suprasellar in four, lobar in three, deep (thalamus and pineal gland) in two, and within the brain stem in two children. Treatment effects of IRS were estimated according to the MacDonald criteria.

Results: A complete response after IRS was seen in four patients, and a partial response was seen in seven patients (median follow-up, 31.5 months). There was no perioperative morbidity after microsurgery and/or IRS, and no radiogenic complications occurred during the follow-up period. Five patients experienced an improvement in their deficits, and no deterioration in neurological/endocrine function was seen in any of the patients at the time of last follow-up evaluation. Conclusion: IRS alone or in combination with microsurgery (in the case of larger tumors) is a safe, effective, and minimally invasive treatment strategy for eloquently located pediatric low-grade gliomas and deserves further prospective evaluation.

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30. Gamma Knife surgery for focal brainstem gliomas

Author(s) Chun P.Y., Sheehan J., Steiner M., Patterson G., Steiner L.

Citation: Journal of Neurosurgery, January 2007, vol./is. 106/1(8-17), 0022-3085;0022-3085 (January 2007)

Publication Date: January 2007

Abstract: Object. Focal tumors, a distinct subgroup of which is composed of brainstem gliomas, may have an indolent clinical course. In the past, their management involved monitoring of open-ended imaging studies and shunt placement if cerebrospinal fluid diversion was required. Nonetheless, their treatment remains a significant challenge for neurosurgeons. Gamma Knife surgery (GKS) has recently been tried as an alternative to surgical extirpation. In the present study the authors assess clinical and imaging results in 20 patients who harbored focal brainstem gliomas treated with GKS between 1990 and 2001. Methods. There were 10 male and 10 female patients with a mean age of 19.1 years. Sixteen tumors were located in the midbrain, three in the pons, and one in the medulla oblongata. The mean tumor volume at the time of GKS was 2.5 cm<sup>3</sup>. In 10 cases a tumor specimen was obtained either by open surgery or stereotactic biopsy, securing the diagnosis of pilocytic astrocytoma in five patients and nonpilocytic astrocytoma in five others. In the remaining 10 cases, the diagnosis was based on clinical and neuroimaging findings. The prescription Gamma Knife dose varied between 10 and 18 Gy, except in three patients who were receiving a boost to a site in which external-beam radiation was previously delivered. An average of four isocenters were utilized per GKS. Patients were followed up for a mean of 78.0 months. The tumors disappeared in four patients and shrank in 12 patients. Of these patients, one experienced transitory extrapyramidal symptoms and fluctuating impairment of consciousness (from somnolence to coma) for 6 months. Another patient whose tumor disappeared 3 years following GKS died of stroke 8 years postoperatively. The rest of the patients either remained stable or improved clinically. Tumor progression occurred in four patients; of these four, one patient developed hydrocephalus requiring a ventriculoperitoneal shunt, two showed neurological deterioration, and one 4-year-old boy died of tumor progression. Conclusions. Gamma Knife surgery may be an effective primary treatment or adjunct to open surgery for focal brainstem gliomas.

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31. Combined treatment of pediatric high-grade glioma with the oncolytic viral strain MTH-68/H and oral valproic acid
The case of a 12-year-old boy with anaplastic astrocytoma of the left thalamus is reported. Postoperative irradiation and chemotherapy could not repress tumor progression; therefore, treatment was undertaken with an oncolytic virus, MTH-68/H, an attenuated strain of Newcastle disease virus (NDV), and valproic acid (VPA), an antiepileptic drug, which also has antineoplastic properties. This treatment resulted in a far-reaching regression of the thalamic glioma, but 4 months later a new tumor manifestation, an extension of the thalamic tumor, appeared in the wall of the IVth ventricle, which required a second neurosurgical intervention. Under continuous MTH-68/H - VPA administration the thalamic tumor remained under control, but the rhombencephalic one progressed relentlessly and led to the fatal outcome. In the final stage, a third tumor manifestation appeared in the left temporal lobe. The possible reasons for the antagonistic behavior of the three manifestations of the same type of glioma to the initially most successful therapy are discussed. The comparative histological study of the thalamic and rhombencephalic tumor manifestations revealed that MTH-68/H treatment induces, similar to in vitro observations, a massive apoptotic tumor cell decline. In the rhombencephalic tumor, in and around the declining tumor cells, NDV antigen could be demonstrated immunohistochemically, and virus particles have been found in the cytoplasm of tumor cells at electron microscopic investigation. These findings document that the oncolytic effect of MTH-68/H treatment is the direct consequence of virus presence and replication in the neoplastic cells. This is the first demonstration of NDV constituents in an MTH-68/H - treated glioma. Copyright Apmis 2006.

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32. Diffuse and focal brain stem tumors in childhood: Prognostic factors and surgical outcome: Experience in a single institution

Author(s) Sandri A., Sardi N., Genitori L., Giordano F., Peretta P., Basso M.E., Bertin D., Mastrodicasa L., Todisco L., Mussa F., Forni M., Ricardi U., Cordero di Montezemolo L., Madon E.

Citation: Child's Nervous System, September 2006, vol./is. 22/9(1127-1135), 0256-7040 (September 2006)

Publication Date: September 2006

Abstract: Objective: Brainstem tumors (BSTs) are usually gliomas and are divided into diffuse BSTs (DBSTs) and focal BSTs (FBSTs). The aim of this study is to investigate the different outcomes of these two entities. Methods: Thirty-one patients with BSTs were admitted to our institution from 1995 to 2003. Patients with DBSTs were treated with locoregional radiotherapy (1.8 Gy/day for 54 Gy) and weekly vincristine for radiosensitization (1.5 mg/sm for six total doses). Patients with FBSTs underwent surgical resection. Chemotherapy and/or radiotherapy were considered in progression. Results and conclusions: Fourteen patients were diagnosed as having DBSTs. The responses to treatment were ten cases of partial response, three of stable disease, and one of progressive disease. General and/or neurological symptoms improved in more than 80% of patients. The median time from diagnosis to progression and to death were, nonetheless, 8 (range of 3-13) and 13 (range of 4-25) months, respectively, with a 2-year overall survival rate of 12.3% [standard error (SE) 11.2]. Seventeen patients were diagnosed as having FBSTs. Gross total removal was achieved in 4/17 cases, subtotal removal in 7/17, and partial removal in 6/17. There was one surgery-related death. Eight out of 17 patients had adjuvant chemo- and/or radiotherapy after progression: 6/8 are without neurological symptoms and 2/8 have died due to tumor progression. The 4-year overall and disease-free survival rates are 87.4 (SE 8.4) and 58.8% (SE 11.9), respectively, the extent of
resection being the most important prognostic factor (p=0.012). DBSTs continue to carry a
dismal prognosis, thus demanding new treatment modalities; FBSTs can be treated
surgically and patients benefit from a better prognosis. Springer-Verlag 2006.

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33. Paediatric brainstem gliomas: Prognostic factors and management

Author(s) Mauffrey C.

Citation: Journal of Clinical Neuroscience, May 2006, vol./is. 13/4(431-437), 0967-5868
(May 2006)

Publication Date: May 2006

Abstract: Background: Although most types of tumours involving the brainstem can be
surgically removed, patients with diffuse pontine brainstem glioma do not benefit from
surgical intervention. The aim of the present study is to establish whether clinical
symptoms, their duration prior to diagnosis, the presence of enhancement on MRI scans
and the histology of the lesion in paediatric brainstem glioma can guide the surgeon in
choosing appropriate management options. Methods: We retrospectively reviewed the
charts and MRI scans of paediatric patients admitted to Turin’s Ospedale Regina
Margherita with a diagnosis of brainstem glioma. Results: Patients with a diffuse pontine
tumour on MRI scan (group 1) had a mean duration of symptoms prior to diagnosis of 2.61
months, 77% had symptoms involving at least one cranial nerve at diagnosis, and no MRI
scans showed enhancement with gadolinium. No patients underwent radical surgery and
84.6% died. For all other patients (group 2), the mean duration of symptoms at diagnosis
was 10.58 months, cranial nerve involvement was present in only 28.5%, and the MRI
scans showed enhancement in 78.6%. Radical surgery was the treatment of choice
(100%). In this study, survival of patients with diffuse pontine brainstem glioma was 25% at
2 years and survival of patients with any other brainstem glioma was 90% at 2 years. 2006
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34. Intratumoral hemorrhage among children with newly diagnosed, diffuse
brainstem glioma

Author(s) Broniscer A., Laningham F.H., Kocak M., Krasin M.J., Fouladi M., Merchant
T.E., Kun L.E., Boyett J.M., Gajjar A.

Citation: Cancer, March 2006, vol./is. 106/6(1364-1371), 0008-543X;1097
(15 Mar
2006)

Publication Date: March 2006

Abstract: BACKGROUND. Children with diffuse brainstem glioma (BSG) commonly
undergo novel therapies because their outcome is poor with radiation therapy (RT).
Although recent clinical trials using new biologic agents documented intratumoral
hemorrhage (IH) among several children with BSG, to the authors’ knowledge little is
known regarding this phenomenon. In the current study, the authors assessed the
characteristics and estimated the cumulative incidence of IH among children with BSG.
METHODS. All available brain imaging studies and medical records of 48 consecutive
patients with newly diagnosed BSG treated at the study institution over a 10-year interval
(1992-2002) were reviewed. Treatment was comprised of RT and various regimens of
conventional chemotherapy; none of these patients received biologic agents. At the time of
last follow-up, all patients had died of tumor progression. RESULTS. The authors reviewed
319 imaging studies (251 magnetic resonance imaging scans and 68 computed
tomography scans). IH was present in 6.25% of patients at the time of diagnosis. The 6-
month and 12-month cumulative incidence estimates of IH regardless of the associated symptoms were 15.5% +/- 5.5% and 24.4% +/- 6.5%, respectively. The same estimates for symptomatic cases were 8.9% +/- 4% and 17.8% +/- 6%, respectively. All cases of IH at the time of diagnosis and 78% of symptomatic cases that developed after diagnosis were located in necrotic areas. CONCLUSIONS. Although IH is uncommon at the time of diagnosis, symptomatic IH may occur among nearly 20% of children after the diagnosis of BSG. The uniform occurrence of IH among patients treated with various chemotherapeutic regimens and its association with necrotic areas suggests that tumor biology plays a significant role in this event. 2006 American Cancer Society.

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35. Targeted therapy with antineoplastons A10 and AS2-1 of high-grade, recurrent, and progressive brainstem glioma

Author(s) Burzynski S.R., Janicki T.J., Weaver R.A., Burzynski B.

Citation: Integrative Cancer Therapies, March 2006, vol./is. 5/1(40-47), 1534-7354;1552-695X (March 2006)

Publication Date: March 2006

Abstract: Background: Brainstem glioma carries the worst prognosis of all malignancies of the brain. Most patients with brainstem glioma fail standard radiation therapy and chemotherapy and do not survive longer than 2 years. Treatment is even more challenging when an inoperable tumor is of high-grade pathology (HBSG). The objective of this report is to summarize the outcome of patients with HBSG treated with antineoplastons in 4 phase 2 trials. Patients: The following group of 18 patients was evaluable: 4 patients with glioblastomas and 14 patients with anaplastic HBSG. Fourteen patients had diffuse intrinsic tumors. Twelve patients suffered from recurrence, and 6 patients did not have radiation therapy or chemotherapy. Methods: Antineoplastons, which consist of antineoplaston A10 (A10I) and AS2-1 injections, were given in escalating doses by intravenous injections. The median duration of antineoplaston administration was 5 months, and the average dosage of A10I was 9.22 g/kg/d and of AS2-1 was 0.31 g/kg/d. Responses were assessed by gadolinium-enhanced magnetic resonance imaging and positron emission tomography. Results: The overall survival at 2 and 5 years was 39% and 22%, respectively, and maximum survival was more than 17 years for a patient with anaplastic astrocytoma and more than 5 years for a patient with glioblastoma. Progression-free survival at 6 months was 39%. Complete response was achieved in 11%, partial response in 11%, stable disease in 39%, and progressive disease in 39% of patients. Antineoplastons were tolerated very well with 1 case of grade 4 toxicity (reversible anemia). Conclusion: Antineoplastons contributed to more than a 5-year survival in recurrent diffuse intrinsic glioblastomas and anaplastic astrocytomas of the brainstem in a small group of patients.

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36. Brain stem tumors in children - Therapeutic results in patients of the University Children's Hospital of Cracow in Poland

Author(s) Korab-Chrzanowska E., Kwiatkowski S., Bartoszewska J.

Citation: Nowotwory, 2005, vol./is. 55/5(367-372), 0029-540X (2005)

Publication Date: 2005

Abstract: Aim. To analyse the treatment results achieved in children treated for brain stem tumours at one institution between the years 1990 and 2004. Material. 20 patients (10 girls, 10 boys) aged 2.8-15.6 years were treated for brain stem tumours at the University Children's Hospital of Cracow (UCHC) in the years 1990-2004. The tumour type was
defined basing on imaging studies (CT, MRI), and, in the case of 7 patients, additionally basing on histopathological results. In the collected material the predominant tumor type was benign glioma, detected in 17 patients. Malignant gliomas were diagnosed in 3 children. Method. 7 children were treated by radiotherapy only. Surgical procedures and adjuvant radiotherapy were employed in 3 patients. 6 children underwent radiotherapy and chemotherapy. Combined surgical treatment followed by radiotherapy and chemotherapy was employed in 4 patients. Results. Of the 20 patients 6 have died (30%). The surviving group (70%) includes 1 patient with tumor progression (5%), 5 - with stable tumors (25%), and 8 (40%) - with tumor regression. The probability of three-year overall survival for the entire group as calculated by the Kaplan-Meier method was 70% while the probability of three-year progression-free survival was 65%. Conclusions. Diffuse brain stem tumors, mostly those involving the pons, and malignant gliomas have poor prognosis. In the presented material we achieved the best treatment results in patients with exophytic or focal tumors, treated surgically with adjuvant therapy.

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37. Direct infiltration of brainstem glioma along the cranial nerves
Author(s) Ree A., Jain R., Rock J., Rosenblum M., Patel S.C.
Citation: Journal of Neuroimaging, April 2005, vol./is. 15/2(197-199), 1051-2284 (April 2005)
Publication Date: April 2005
Abstract: The authors describe a case of a low-grade brainstem glioma extending along the cranial nerves without any evidence of leptomeningeal spread. The tumor extended directly along the VII-VIIIth cranial nerve complex and also along the trigeminal nerve, which is quite an unusual characteristic of the glial tumors. Copyright 2005 by the American Society of Neuroimaging.
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38. Central neurogenic hyperventilation and lactate production in brainstem glioma
Author(s) Gaviani P., Gonzalez R.G., Zhu J.-J., Batchelor T.T., Henson J.W.
Citation: Neurology, January 2005, vol./is. 64/1(166-167), 0028-3878 (11 Jan 2005)
Publication Date: January 2005
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39. Supratentorial High-Grade Astrocytoma and Diffuse Brainstem Glioma: Two Challenges for the Pediatric Oncologist
Author(s) Broniscer A., Gajjar A.
Citation: Oncologist, 2004, vol./is. 9/2(197-206), 1083-7159 (2004)
Publication Date: 2004
Abstract: Pediatric high-grade gliomas represent a heterogeneous group of tumors that accounts for 15%-20% of all pediatric central nervous system tumors. These neoplasms predominantly involve the supratentorial hemispheres or the pons, in which case the tumors are usually called diffuse brainstem gliomas. The diagnosis of supratentorial neoplasms is dependent on their histologic appearance. The maximum possible surgical resection is always attempted since the degree of surgical resection is the main prognostic factor for these patients. Older children (>3 years) with supratentorial neoplasms undergo a multimodality treatment comprised of surgical resection, radiation therapy, and chemotherapy. The addition of chemotherapy seems to improve the survival of a subset of these children, particularly those with glioblastoma multiforme. However, 2-year survival
rates remain poor for children with supratentorial neoplasms, ranging from 10%-30%. The diagnosis of a diffuse brainstem glioma is based upon typical imaging, dispensing with the need for surgery in the majority of cases. Radiation therapy is the mainstay of treatment for children with diffuse brainstem gliomas. The role of chemotherapy for these children is not clear, and it is, in general, employed in the context of an investigational study. Less than 10% of children with diffuse brainstem gliomas survive 2 years. Because the outcome for patients with either type of tumor is poor when standard multimodality therapy is used, these children are ideal candidates for innovative treatment approaches.

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40. A phase I trial of etanidazole and hyperfractionated radiotherapy in children with diffuse brainstem glioma


Citation: International Journal of Radiation Oncology Biology Physics, April 2003, vol./is. 55/5(1182-1185), 0360-3016 (01 Apr 2003)

Publication Date: April 2003

Abstract: Purpose: To determine the toxicity and maximum tolerated dose of etanidazole administered concurrently with hyperfractionated radiation therapy (HRT) for children with brainstem glioma. Methods and Materials: Eighteen patients with brainstem glioma were treated with etanidazole and HRT on a dose escalation protocol (Phase I trial) between 1990 and 1996. All patients had MRI confirmation of diffuse pontine glioma and signs/symptoms of cranial nerve deficit, ataxia, or long tract signs of <6 months' duration. Cervicomedullary tumors were excluded. Patients (median age: 8.5 years; 11 males, 7 females) received HRT to the tumor volume plus a 2-cm margin with parallel-opposed 6-15-MV photons. The total dose was 66 Gy in 44 fractions (1.5 Gy b.i.d., with at least 6 h between fractions) for the first 3 patients and 63 Gy in 42 fractions for the subsequent 15 patients. Etanidazole was administered as a rapid i.v. infusion 30 min before the morning fraction of HRT. Planned doses of etanidazole were 1.8 g/m<sup>2</sup> x 17 doses (30.6 g/m<sup>2</sup>) at Step 1 to a maximum of 2.4 g/m<sup>2</sup> x 21 doses (50.4 g/m<sup>2</sup>) at Step 8. Dose escalation was planned with 3 patients at each of the 8 levels. Results: Three patients were treated at each dose level except Level 2, on which only 1 patient was treated. The highest dose level achieved was Level 7, which delivered a total etanidazole dose of 46.2 g/m<sup>2</sup>. Two patients were treated at this level, and both patients experienced Grade 3 toxicity in the form of a diffuse cutaneous rash. Three patients received a lower dose of 42 g/m<sup>2</sup> (dose Level 6) without significant toxicity, and this represents the maximum tolerated dose (MTD). There were 23 cases of Grade 1 toxicity (10 vomiting, 5 peripheral neuropathy, 2 rash, 2 constipation, 1 weight loss, 3 others), 11 cases of Grade 2 toxicity (4 vomiting, 2 skin erythema, 2 constipation, 1 arthralgia, 1 urinary retention, 1 hematologic), and 4 Grade 3 toxicities (2 rash, 1 vomiting, 1 skin desquamation). Grade 2 or 3 peripheral neuropathy was not seen at any dose level. The median survival from the start of treatment was 8.5 months (range: 3-58 months). Conclusion: The MTD of etanidazole in children receiving HRT for brainstem glioma is 42 g/m<sup>2</sup>, with cutaneous rash as the dose-limiting toxicity. This is in contrast to the adult experience, which demonstrates a 24% lower MTD of 34 g/m<sup>2</sup> limited by peripheral neuropathy. 2003 Elsevier Science Inc.

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41. Phase II study of antineoplaston A10 and AS2-1 in patients with recurrent diffuse
intrinsic brain stem glioma: A preliminary report


Citation: Drugs in R and D, 2003, vol./is. 4/2(91-101), 1174-5886 (2003)

Publication Date: 2003

Abstract: Objective: A phase II study of antineoplaston A10 and AS2-1 was conducted to evaluate the antineoplastic activity in patients with recurrent diffuse intrinsic brain stem glioma. Patients and methods: This report describes the results of treatment of the first 12 patients admitted to the study. Patients received escalating doses of antineoplaston A10 and AS2-1 by intravenous bolus injections. The median duration of treatment was 6 months and the average dosage of antineoplaston A10 was 11.3 g/kg/day and of antineoplaston AS2-1 0.4 g/kg/day. Responses were assessed by gadolinium-enhanced magnetic resonance imaging of the head. Results: Of ten evaluable patients, complete response was determined in two cases (20%), partial response in three (30%), stable disease in three (30%) and progressive disease in two (20%). Survival at 2 years was 33.3%. Currently, of all 12 patients, two (17%) were alive and tumour free for over 5 years since initial diagnosis; one was alive for more than 5 years, and another for more than 4 years from the start of treatment. Only mild and moderate toxicities were observed, which included three cases of skin allergy, two cases of anaemia, fever and hypernatraemia, and single cases of agranulocytosis, hypoglycaemia, numbness, tiredness, myalgia and vomiting. Conclusion: The results of this study compared favourably with the responses of patients treated with radiation therapy and chemotherapy. The study continues with accrual of additional patients.

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42. Pediatric glial tumors

Author(s) Cohen K.J., Broniscer A., Glod J.

Citation: Current treatment options in oncology, December 2001, vol./is. 2/6(529-536), 1527-2729 (Dec 2001)

Publication Date: December 2001

Abstract: Glial neoplasms in children comprise many heterogeneous tumors that include pilocytic and fibrillary astrocytomas, ependymomas, and the diffuse intrinsic pontine gliomas. In contrast to adults, most of whom present with high-grade fibrillary neoplasms, alternate histologies represent most cases seen in the pediatric setting. In addition, although most adult gliomas are supratentorial in location, in pediatrics infratentorial tumors (posterior fossa and brain stem) predominate. We discuss three specific tumors: diffuse intrinsic pontine gliomas; pilocytic astrocytomas; and ependymomas. Maximal surgical resection is the mainstay of therapy for both pilocytic astrocytomas and ependymomas. Failure to achieve an optimal resection often results in progression and the need for further therapy for patients with pilocytic astrocytomas, and is ultimately fatal in most children with subtotally resected ependymomas. Surgical resection has no role in the treatment of pontine gliomas. Focal radiation therapy is included routinely in the treatment of ependymomas, and it has been shown to improve event-free survival. This therapy also is used in the treatment of pontine gliomas because radiation treatment appears to slow inevitable tumor progression. Radiation therapy in pilocytic astrocytomas is generally reserved for patients who progress after an initial surgical resection or for those patients with midline tumors; these patients are poor candidates for aggressive surgical resection. The role of chemotherapy in these tumors is in evolution. Chemotherapy for pilocytic astrocytomas, particularly in young children (for whom radiation therapy is avoided), appears to be effective in the treatment of a subset of patients. Up-front chemotherapy is generally reserved for the youngest children who present with ependymoma. In the recurrence setting, chemotherapy has shown some activity, although this approach is never curative. Despite the application of various chemotherapeutics and other biologic agents,
none of these therapies has improved the prognosis for patients with the uniformly lethal pontine glioma.

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43. Brainstem gliomas in adults: Prognostic factors and classification


Citation: Brain, 2001, vol./is. 124/12(2528-2539), 0006-8950 (2001)

Publication Date: 2001

Abstract: In contrast to childhood brainstem gliomas, adult brainstem gliomas are rare and poorly understood. The charts of 48 adults suffering from brainstem glioma were reviewed in order to determine prognostic factors, evaluate the effect of treatment and propose a classification of these tumours. Mean age at onset was 34 years (range 16-70 years). The main presenting symptoms were gait disturbance (61%), headache (44%), weakness of the limbs (42%) and diplopia (40%). Four patterns were identified on MRI, representing non-enhancing, diffusely infiltrative tumours (50%), contrast-enhancing localized masses (31%), isolated tectal tumours (8%) and other patterns (11%). Treatment consisted of partial resection (8%), radiotherapy (94%) and chemotherapy (56%). Overall median survival was 5.4 years. On univariate analysis, the following favourable prognostic factors were identified (P < 0.01): age of onset <40 years, duration of symptoms before diagnosis >3 months, Karnofski performance status >70, low-grade histology, absence of contrast enhancement and 'necrosis' on MRI. On multivariate analysis, the duration of symptoms, the appearance of 'necrosis' on MRI and the histological grade of the tumour remained significant and independent prognostic factors (P < 0.05). Eighty-five percent of the tumours could be classified into one of the following three groups on the basis of clinical, radiological and histological features. (i) Diffuse intrinsic low-grade gliomas (46%) usually occurred in young adults with a long clinical history before diagnosis and a diffusely enlarged brainstem on MRI that did not show contrast enhancement. These patients were improved by radiotherapy in 62% of cases and had a long survival time (median 7.3 years). Anaplastic transformation (appearance of contrast enhancement, 27%) and relentless growth without other changes (23%) were the main causes of death. (ii) Malignant gliomas (31%) occurred in elderly patients with a short clinical history. Contrast enhancement and necrosis were the rule on MRI. These tumours were highly resistant to treatment and the patients had a median survival time of 11.2 months. (iii) Focal tectal gliomas (8%) occurred in young patients and were often revealed by isolated hydrocephalus. The course was indolent and the projected median survival period exceeded 10 years. In conclusion, adult brainstem gliomas are different from the childhood forms and resemble supratentorial gliomas in adults. Low-grade tumours have a clinicoradiological pattern that is so characteristic that the need for a potentially harmful biopsy is debatable. The optimum timing of treatment for supratentorial low-grade tumours remains unclear. In high-grade gliomas, the prognosis remains extremely poor despite aggressive treatment with radiotherapy and chemotherapy.

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44. Treatment of a patient by vaccination with autologous dendritic cells pulsed with allogeneic major histocompatibility complex class I-matched tumor peptides. Case Report

Author(s) Liau L.M., Black K.L., Martin N.A., Sykes S.N., Bronstein J.M., Jouben-Steele L., Mishcel P.S., Belidegrun A., Cloughesy T.F.

Citation: Neurosurgical focus, 2000, vol./is. 9/6(e8), 1092-0684 (2000)
Abstract: Dendritic cells (DCs) are antigen-presenting cells that play a central role in the initiation and modulation of antitumor immune responses. In this pilot study, we investigated the ability of autologous DCs pulsed ex vivo with allogeneic major histocompatibility complex class I-matched glioblastoma peptides to stimulate host antitumor immune responses when injected as a vaccine. A patient with recurrent brainstem glioblastoma multiforme (GBM) received a series of three intradermal immunizations of antigen-pulsed DCs on an outpatient basis following surgical debulking of her posterior fossa tumor. Dendritic cell vaccination was well tolerated, and no clinical signs of autoimmunity or experimental allergic encephalomyelitis were detected. She developed a measurable cellular immune response against the allogeneic glioblastoma peptides used in her vaccine preparation, as demonstrated by in vitro T-cell proliferation assays. In addition, increased T-cell infiltration was noted within the intracranial tumor site in the biopsy sample obtained following DC vaccination. An objective clinical response, however, was not evident, and this patient eventually died 21 months after her disease was diagnosed. To our knowledge, this is the first patient with brain cancer ever to be treated with DC-based immunotherapy. This case illustrates that vaccination with DCs pulsed with acid-eluted glioblastoma peptides is feasible and can induce systemic antigen-specific immunity in a patient with recurrent GBM. Additional studies are necessary to determine the optimum DC doses and antigen loading conditions that may translate into clinical effectiveness and survival benefit for patients with brain tumors. Phase I trials for malignant glioma are currently underway.

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45. Radiosurgery in the management of pediatric brain tumors

Author(s) Raco A., Raimondi A.J., D'Alonzo A., Esposito V., Valentino V.

Citation: Child's Nervous System, May 2000, vol./is. 16/5(287-295), 0256-7040 (May 2000)

Publication Date: May 2000

Abstract: A total of 114 patients with benign and malignant intracranial tumors were treated by Valentino at the Flaminia Radiosurgical Center using a Philips 6-MeV linear accelerator between 1987 and 1995. The tumor locations break down as follows: 36 in the cerebral hemispheres, 14 in the region of the hypothalamus/optic chiasm, 21 in the III ventricle/pineal region, 3 in the basal ganglia, 27 in the posterior fossa, 13 in the brainstem. Seventy-nine patients had multivariate/combined treatment consisting of surgery or biopsy followed by chemotherapy, radiotherapy and/or radiosurgery. Thirty-five were not operated on or biopsied but were treated primarily by radiosurgery, which was associated with chemotherapy and conventional radiotherapy. The short- and long-term results were evaluated separately for each pathology in an attempt to derive guidelines for future treatment. For tumors of the pineal region, we are of the opinion that radiosurgery is the treatment of choice in children and that more than one-third of patients can be cured by this means. The remaining patients require surgery and/or chemotherapy in addition. For medulloblastomas radiosurgery may be useful to control local recurrence if coupled with chemotherapy. In the case of ependymomas, partly because of the extreme malignancy of the lesions in our series, radiosurgery did not succeed in controlling local recurrence. We fear that limiting treatment to radiosurgery, rather than prescribing conventional radiotherapy when indicated, could permit CNS seeding. For craniopharyngiomas radiosurgery proved useful for controlling solid remnants. In glial tumors radiosurgery helped either to 'sterilize' the tumor bed after removal or to treat remnants of the lesions in critical areas; for diffuse brain stem gliomas it should be considered the treatment of choice.

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46. Surgical treatment of primary midbrain gliomas
Author(s) Wang C., Zhang J., Liu A., Sun B., Zhao Y.

Citation: Surgical Neurology, January 2000, vol./is. 53/1(41-51), 0090-3019 (January 2000)

Publication Date: January 2000

Abstract: BACKGROUND: The treatment of brainstem gliomas remains controversial. This article focuses on surgical results. METHODS: The authors retrospectively analyzed 35 patients with primary midbrain gliomas who were treated at Beijing Neurosurgical Institute from 1986 to 1997. The diagnosis was verified by histological examination. RESULT: The incidence of midbrain glioma was 10.3% (35/340) in our patients with brain stem tumors. The 35 gliomas were classified into three therapeutic groups by their locations: 7 were located in the tectal region, 8 in the aqueductal region, and 20 in the tegmental region. All of the patients underwent microsurgical treatment based on a minimally invasive approach. The operation took the form of total resection in 19 cases, subtotal resection in 12, and partial resection in 4. The operative mortality was 0. With a mean follow-up of 28 months (range, 6-48 months), 65.7% (23/35) of patients could live independently. CONCLUSION: The volume and location of midbrain tumors were highly correlated with outcome. The resection of as much tumor as possible was optimal for the treatment of midbrain gliomas and radiotherapy after operation was beneficial to patients. Copyright (C) 2000 Elsevier Science Inc.

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47. Diffuse medulla oblongata and pontine gliomas in childhood: A review of 37 cases

Author(s) Carrie C., Negrier S., Gomez F., Thiesse P., Mottolese C., Frappaz D., Bouffet E.

Citation: Electronic Journal of Oncology, 1999, vol./is. /2(111-125), 1292-8933 (1999)

Publication Date: 1999

Abstract: From 1975 to 1997, thirty seven newly diagnosed children aged 2 mos. to 14.3 years with diffuse medulla oblongata or pontine tumours were referred to the Centre Leon Berard. Surgical biopsies were performed in 9 patients. All but one received radiation therapy. The mean dose of radiation was 53 Gy. Thirty two received chemotherapy. All patients died, one from related toxicity, and the rest from progressive disease. Relapses always occurred in the radiotherapy field. Medulla oblongata and pontine tumours would appear to have the worst outcome of all brain stem gliomas and should be separately analysed.

Source: EMBASE


Author(s) Dario A., Iadini A., Cerati M., Marra A., Dorizzi A.

Citation: Rivista di Neurobiologia, 1998, vol./is. 44/1(45-50), 0035-6336 (1998)

Publication Date: 1998

Abstract: The brainstem gangliogliomas are rare with only 32 cases reported in literature. A case of this tumour in a 4-year-old child with focal symptoms and a sudden neurological worsening is described. After complete removal of the tumour the outcome was poor. The preoperative CT-scans and postoperative MRI are presented. The clinical presentation, the course, the radiological findings, the treatment and the prognosis of this uncommon neoplasm are debated in relation with the data from the previous cases.

Source: EMBASE

49. The management of brainstem gliomas in patients with neurofibromatosis 1
Author(s): Pollack I.F., Shultz B., Mulvihill J.J.

Citation: Neurology, June 1996, vol./is. 46/6(1652-1660), 0028-3878 (June 1996)

Publication Date: June 1996

Abstract: The appropriate management of brainstem tumors in patients with neurofibromatosis 1 (NF1) has been problematic because the natural history of these lesions remains poorly defined. To formulate rational guidelines for the evaluation and treatment of these tumors, we reviewed the outcome of 21 patients with brainstem mass lesions followed in our NF clinic during the last 9 years. We subdivided the imaging features of these lesions into four groups: (1) diffuse enlargement of the brainstem with hypointensity on T$_1$-weighted MR images and hyperintensity on T$_2$-weighted images (n = 9); (2) focal enhancing masses (n = 7); (3) intrinsic tectal tumors (n = 5); and (4) focal nonenhancing areas of hypointensity on T$_1$-weighted MR images (n = 2). Two cases exhibited two types of lesions. Twelve patients presented with, or developed, symptoms that were referable to the mass; in nine, the lesion was asymptomatic. A distinguishing feature of these tumors was their generally indolent biological behavior. With a median follow-up of 3.75 years, only 10 patients have had radiographic (n = 9) or clinical (n = 3) evidence of disease progression. In seven of these patients, the tumor subsequently stabilized in size or regressed without intervention. Only four patients, each with a focal enhancing tumor, received specific therapy for the tumor; this consisted of biopsy (n = 1), excision (n = 3), and adjuvant radiotherapy (n = 2). Each of these lesions was a low-grade glioma histologically and each remained stable in size after treatment (median follow-up = 4.25 years). Four patients with tectal tumors underwent insertion of a CSF shunt for hydrocephalus, but required no specific treatment for the tumor. None of the patients with diffuse brainstem lesions or focal areas of hypointensity required any intervention for the tumor. All 21 patients are presently alive and well. We conclude that the biological behavior of brainstem lesions in patients with NF1 differs significantly from that of lesions with a similar appearance in patients without this disorder. Although these lesions may at some time in their course exhibit clinical and radiographic progression, most do not require specific intervention. The lesions that are most likely to progress and require therapy are focal enhancing tumors; however, even lesions in this subgroup may stabilize in size or regress spontaneously without intervention. Based on these results, we recommend that intervention be limited to those lesions that exhibit rapid or unrelenting growth on serial images or that produce significant clinical deterioration.

Source: EMBASE

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50. Anaplastic ganglioglioma in children.

Author(s) Karremann M, Pietsch T, Janssen G, Kramm CM, Wolff JE

Citation: Journal of Neuro-Oncology, April 2009, vol./is. 92/2(157-63), 0167-594X;1573-7373 (2009 Apr)

Publication Date: April 2009

Abstract: PURPOSE: Anaplastic gangliogliomas (AGG) are gangliogliomas with areas of pronounced hypercellularity, vascular proliferation, necrosis, and many mitotic figures. As very few pediatric patients have been studied, we analyzed the cases registered in the HIT-GBM database. PATIENTS AND METHODS: Patient data were obtained from the German HIT-GBM database. Inclusion criteria were diagnosis of AGG proven by a central neuropathological review and patient age 0 to 17 years. Eight patients (five male and three female) were identified. RESULTS: Patients’ median age was 10 years. The median history of disease was 9 months (range, 1.0-43.0 months). Initial symptoms included signs of raised intracranial pressure, seizures, and, in the case of spinal cord tumor, bladder dysfunction. In five cases, AGGs were localized supratentorially with three patients having multiple lobes involved. The tumors affected the frontal (n = 3 cases), parietal (n = 2), temporal (n = 2), and occipital lobes (n = 1), as well as the brainstem (n = 1) and the spinal cord (n = 2). Gross total tumor resection was achieved in six patients. The estimated 5-year overall survival rate +/- standard error was 88 +/- 12%, and the event-free survival rate was 63 +/- 17%. While gender and tumor location did not affect survival rates, gross total tumor
resection provided a better overall survival than non-total resection. CONCLUSION: The prognosis of pediatric patients with AGG is good, especially for those who undergo gross total tumor resection.

Source: Medline
Available in print at ULHT journal article requests. Complete the online form to obtain articles.

52. Brainstem ganglioglioma.
Author(s) Mpairamidis E, Alexiou GA, Stefanaki K, Sfakianos G, Prodromou N
Citation: Journal of Child Neurology, December 2008, vol./is. 23/12(1481-3), 0883-0738:1708-8283 (2008 Dec)
Publication Date: December 2008
Abstract: Gangliogliomas are usually benign slow-growing neoplasms, seen mainly in the first 3 decades of life and are prevalently located supratentorial, mostly in the temporal and frontal lobe. The authors present a rare case of a brainstem ganglioglioma in an 11-year-old boy who was referred to their hospital complaining of episodes of blurry vision, loss of memory, gait disturbances, and morning headache with vomiting, lasting for over a month. Computed tomography and magnetic resonance imaging scans revealed a mass on the dorsal surface of the brainstem, compressing the brainstem and producing secondary obstructive hydrocephalus. The patient was operated upon, and the histopathology revealed the presence of a ganglioglioma grade II (World Health Organization classification). On follow-up examination after 1 year, a minor gait imbalance was the only finding. A total resection should be always attempted, where possible in brainstem gangliogliomas. Close follow-up is mandatory, and re-resection or radiotherapy should be considered in case of tumor recurrence.
Source: Medline
Available in print at ULHT journal article requests. Complete the online form to obtain articles.

Author(s) Milligan BD, Giannini C, Link MJ
Citation: Journal of Neurosurgery, October 2007, vol./is. 107/4 Suppl(292-6), 0022-3085;0022-3085 (2007 Oct)
Publication Date: October 2007
Abstract: The authors report a case of a posterior fossa ganglioglioma centered in the cerebellopontine angle occurring in a child. As with cortically based gangliogliomas, the primary therapy is resection. When the tumor presents in the posterior fossa, often only partial resection can be accomplished without significant neurological deficit. The role of adjuvant chemotherapy and radiation therapy remains controversial, although these are usually reserved for high-grade lesions or progressive growth. The literature regarding the natural history, surgical outcomes, and indications for adjuvant therapy is reviewed. Although it occurs rarely, ganglioglioma should be included in the differential diagnosis of a posterior fossa mass in a child or young adult.
Source: Medline
Available in print at ULHT journal article requests. Complete the online form to obtain articles.

Author(s) Sandri A, Sardi N, Genitori L, Giordano F, Peretta P, Basso ME, Bertin D, Mastrodicasa L, Todisco L, Mussa F, Forni M, Ricardi U, Cordero di Montezemolo L,
OBJECTIVE: Brainstem tumors (BSTs) are usually gliomas and are divided into diffuse BSTs (DBSTs) and focal BSTs (FBSTs). The aim of this study is to investigate the different outcomes of these two entities. METHODS: Thirty-one patients with BSTs were admitted to our institution from 1995 to 2003. Patients with DBSTs were treated with locoregional radiotherapy (1.8 Gy/day for 54 Gy) and weekly vincristine for radiosensitization (1.5 mg/sm for six total doses). Patients with FBSTs underwent surgical resection. Chemotherapy and/or radiotherapy were considered in progression. RESULTS AND CONCLUSIONS: Fourteen patients were diagnosed as having DBSTs. The responses to treatment were ten cases of partial response, three of stable disease, and one of progressive disease. General and/or neurological symptoms improved in more than 80% of patients. The median time from diagnosis to progression and to death were, nonetheless, 8 (range of 3-13) and 13 (range of 4-25) months, respectively, with a 2-year overall survival rate of 12.3% [standard error (SE) 11.2]. Seventeen patients were diagnosed as having FBSTs. Gross total removal was achieved in 4/17 cases, subtotal removal in 7/17, and partial removal in 6/17. There was one surgery-related death. Eight out of 17 patients had adjuvant chemo- and/or radiotherapy after progression: 6/8 are without neurological symptoms and 2/8 have died due to tumor progression. The 4-year overall and disease-free survival rates are 87.4 (SE 8.4) and 58.8% (SE 11.9), respectively, the extent of resection being the most important prognostic factor (p=0.012). DBSTs continue to carry a dismal prognosis, thus demanding new treatment modalities; FBSTs can be treated surgically and patients benefit from a better prognosis.

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Abstract: BACKGROUND: Brainstem gangliogliomas are rare low-grade tumors that usually have a long clinical history. However, they may cause sudden death. There are only 31 cases of brainstem ganglioglioma reported in the literature, and only one has been studied with magnetic resonance (MR). We present three new cases of brainstem ganglion cell tumor studied with computed tomography (CT) (3 cases) and MR (2 cases) and discuss the clinical presentation, diagnostic imaging and treatment of these tumors.

CASE DESCRIPTION: Age at presentation ranged from 19 to 59 years old. Two patients were female and 1 male. Duration of symptoms before diagnosis ranged from 1 year to nearly 14 years. Presenting complaints included syncope spells, cranial nerve deficits, headache, and gait instability. Imaging studies revealed well-circumscribed lesions involving the brainstem; the lesion was cystic in one case and calcified in one. They were iso- or hyperdense on CT scan, isodense on T1-weighted and hyperdense on T2-weighted MRI and frequently showed contrast enhancement. All tumors were operated through a posterior fossa craniectomy. Using microsurgical techniques only partial resection could be achieved, as there was no sharp delineation from the surrounding tissue in any case. Two of our patients had increased neurological deficits after surgery. Radiotherapy was not given. Follow-up of tumoral remnants has not shown clear tumor growth after 1, 3.5, and 10 years.

CONCLUSIONS: Imaging characteristics of brainstem gangliogliomas do not seem to differ from those in other locations and are not specific. Radical surgery is rarely if ever possible, nor is it advisable because of the risk of functional deterioration. However, because of their benign histology, partial resection seems to carry a similar prognosis as tumors in other locations that are amenable to complete resection.
navigation, ultrasound and monitoring plays an important role for focal brainstem lesions. Focal/conformal radiotherapy has an adjuvant role but better treatments are needed for the diffuse pontine brainstem lesions. Copyright 2001 S. Karger AG, Basel

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59. Trigeminal ganglioneuroma.
Author(s) Abe T, Asano T, Manabe T, Matsuura H, Furuta T, Taguchi K
Citation: Brain Tumor Pathology, 1999, vol./is. 16/1(49-53), 1433-7398;1433-7398 (1999)
Publication Date: 1999
Abstract: We present the case of an 8-year-old girl with a gangliioneuroma in the left cerebellopontine angle region. The tumor originated from the sensory root of the trigeminal nerve. Histopathologically, it was composed of neoplastic ganglion cells and Schwann cells, leading us to the diagnosis of gangliioneuroma. Intracranial gangliioneuroma is very rare. To our knowledge, this is the first report of a trigeminal gangliioneuroma. The nature and origin of this tumor are discussed and the literature reviewed.
Source: Medline
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60. Ganglioglioma of the brain stem: neurological dysfunction of 16-year duration.
Author(s) Karamitopoulou E, Perentes E, Probst A, Wegmann W
Citation: Clinical Neuropathology, May 1995, vol./is. 14/3(162-8), 0722-5091;0722-5091 (1995 May-Jun)
Publication Date: May 1995
Abstract: An autopsy case of a brain stem ganglioglioma in a 38-year-old male patient with neurological dysfunction of 16-year duration is reported. Immunohistochemical investigation of the tumor was performed using a panel of antibodies against neurofilament protein (NFP), synaptophysin (SY 38), beta-tubulin (TUJ1), neuron specific enolase (NSE), and glial fibrillary acidic protein (GFAP). The value of these markers in the establishment of the diagnosis, as well as the general features, the prognosis and the therapeutic approach of the gangliogliomas are discussed.
Source: Medline
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61. Brain tumor therapy-induced changes in normal-appearing brainstem measured with longitudinal diffusion tensor imaging
Author(s) Hua C., Merchant T.E., Gajjar A., Broniscer A., Zhang Y., Li Y., Glenn G.R., Kun L.E., Ogg R.J.
Citation: International Journal of Radiation Oncology Biology Physics, April 2012, vol./is. 82/5(2047-2054), 0360-3016;1879-355X (01 Apr 2012)
Publication Date: April 2012
Abstract: Purpose: To characterize therapy-induced changes in normal-appearing brainstems of childhood brain tumor patients by serial diffusion tensor imaging (DTI). Methods and Materials: We analyzed 109 DTI studies from 20 brain tumor patients, aged 4 to 23 years, with normal-appearing brainstems included in the treatment fields. Those with
medulloblastomas, supratentorial primitive neuroectodermal tumors, and atypical teratoid rhabdoid tumors \((n = 10)\) received postoperative craniospinal irradiation \((23.4-39.6 \text{ Gy})\) and a cumulative dose of 55.8 Gy to the primary site, followed by four cycles of high-dose chemotherapy. Patients with high-grade gliomas \((n = 10)\) received erlotinib during and after irradiation \((54-59.4 \text{ Gy})\). Parametric maps of fractional anisotropy \((FA)\) and apparent diffusion coefficient \((ADC)\) were computed and spatially registered to three-dimensional radiation dose data. Volumes of interest included corticospinal tracts, medial lemnisci, and the pons. Serving as an age-related benchmark for comparison, 37 DTI studies from 20 healthy volunteers, aged 6 to 25 years, were included in the analysis. Results: The median DTI follow-up time was 3.5 years \((\text{range}, 1.6-5.0 \text{ years})\). The median mean dose to the pons was 56 Gy \((\text{range}, 7-59 \text{ Gy})\). Three patterns were seen in longitudinal FA and apparent diffusion coefficient changes: (1) a stable or normal developing time trend, (2) initial deviation from normal with subsequent recovery, and (3) progressive deviation without evidence of complete recovery. The maximal decline in FA often occurred 1.5 to 3.5 years after the start of radiation therapy. A full recovery time trend could be observed within 4 years. Patients with incomplete recovery often had a larger decline in FA within the first year. Radiation dose alone did not predict long-term recovery patterns. Conclusions: Variations existed among individual patients after therapy in longitudinal evolution of brainstem white matter injury and recovery. Early response in brainstem anisotropy may serve as an indicator of the recovery time trend over 5 years after radiation therapy. 2012 Elsevier Inc.

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62. A phase II study of O6-benzylguanine and temozolomide in pediatric patients with recurrent or progressive high-grade gliomas and brainstem gliomas: A Pediatric Brain Tumor Consortium study


Citation: Journal of Neuro-Oncology, February 2012, vol./is. 106/3(643-649), 0167-594X;1573-7373 (February 2012)

Publication Date: February 2012

Abstract: To estimate the sustained \((\geq 8 \text{ weeks})\) objective response rate in pediatric patients with recurrent or progressive high-grade gliomas \((\text{HGG, Stratum A})\) or brainstem gliomas \((\text{BSG, Stratum B})\) treated with the combination of O<sup>6</sup>-benzylguanine \((\text{O6BG})\) and temozolomide \((\text{TMZ})\). Patients received O6BG 120 mg/m<sup>2</sup>/d IV followed by TMZ 75 mg/m<sup>2</sup>/d orally daily for 5 consecutive days of each 28-day course. The target objective response rate to consider the combination active was 17%. A two-stage design was employed. Forty-three patients were enrolled; 41 were evaluable for response, including 25 patients with HGG and 16 patients with BSG. The combination of O6BG and TMZ was tolerable, and the primary toxicities were myelosuppression and gastrointestinal symptoms. One sustained \((\geq 8 \text{ weeks})\) partial response was observed in the HGG cohort; no sustained objective responses were observed in the BSG cohort. Long-term \((\geq 6 \text{ courses})\) stable disease \((\text{SD})\) was observed in 4 patients in Stratum A and 1 patient in Stratum B. Of the 5 patients with objective response or longterm SD, 3 underwent central review with 2 reclassified as low-grade gliomas. The combination of O6BG and TMZ did not achieve the target response rate for activity in pediatric patients with recurrent or progressive HGG and BSG. 2011 Springer Science+Business Media, LLC. (outside the USA).

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63. Human adipose tissue-derived mesenchymal stem cells: Characteristics and therapeutic potential as cellular vehicles for prodrug gene therapy against brainstem...
gliomas

Author(s) Choi S.A., Lee J.Y., Wang K.-C., Phi J.H., Song S.H., Song J., Kim S.-K.

Citation: European Journal of Cancer, January 2012, vol./is. 48/1(129-137), 0959-8049;1879-0852 (January 2012)

Publication Date: January 2012

Abstract: Human mesenchymal stem cells (hMSCs) have emerged as attractive cellular vehicles for gene therapy against brain malignancy because of their targeted tropism for cancer and the intrinsic attribute of autologous transplantation. We evaluated the characteristics and therapeutic potential of human adipose tissue-derived MSCs (hAT-MSCs) and prodrug gene therapy against diffuse pontine gliomas. The hAT-MSCs were isolated from human adipose tissue and characterised for morphology, surface markers and potential to differentiate into mesenchymal and neuronal lineages. We genetically modified hAT-MSCs to express rabbit carboxylesterase (rCE) enzyme, which can efficiently convert the prodrug CPT-11 (irinotecan-7-ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxycamptothecin), into the active drug SN-38 (7-ethyl-10-hydroxycamptothecin). The migratory capacity of hAT-MSCs expressing rCE (hAT-MSC.rCE), their ability to convert CPT-11 to SN-38 and cytotoxic effect on F98 cells were evaluated in vitro. The therapeautic potential of hAT-MSC.rCE was confirmed using a rat brainstem glioma model. The hAT-MSCs showed fibroblast-like morphology and expressed hMSC-specific markers including CD73, CD90 and CD105. The hAT-MSCs could differentiate into a mesenchymal lineage and transdifferentiate into a neuronal lineage under optimum culture conditions. The hAT-MSC.rCE converted CPT-11 to SN-38 and preserved the tumour tropism of hAT-MSCs. Brainstem glioma-bearing rats treated with hAT-MSC.rCE and CPT-11 survived 5 d more than rats treated with CPT-11 only (p = 0.0018). Our study demonstrates that hAT-MSCs can be easily prepared and genetically modified as cellular vehicles for prodrug gene therapy and that they have therapeutic potential against brainstem gliomas. 2011 Elsevier Ltd. All rights reserved.

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64. Metabolic management of brain cancer

Author(s) Seyfried T.N., Kiebish M.A., Marsh J., Shelton L.M., Huysentruyt L.C., Mukherjee P.

Citation: Biochimica et Biophysica Acta - Bioenergetics, June 2011, vol./is. 1807/6(577-594), 0005-2728 (June 2011)

Publication Date: June 2011

Abstract: Malignant brain tumors are a significant health problem in children and adults. Conventional therapeutic approaches have been largely unsuccessful in providing long-term management. As primarily a metabolic disease, malignant brain cancer can be managed through changes in metabolic environment. In contrast to normal neurons and glia, which readily transition to ketone bodies (beta-hydroxybutyrate) for energy under reduced glucose, malignant brain tumors are strongly dependent on glycolysis for energy. The transition from glucose to ketone bodies as a major energy source is an evolutionary conserved adaptation to food deprivation that permits the survival of normal cells during extreme shifts in nutritional environment. Only those cells with a flexible genome and normal mitochondria can effectively transition from one energy state to another. Mutations restrict genomic and metabolic flexibility thus making tumor cells more vulnerable to energy stress than normal cells. We propose an alternative approach to brain cancer management that exploits the metabolic flexibility of normal cells at the expense of the genetically defective and metabolically challenged tumor cells. This approach to brain cancer management is supported from recent studies in mice and humans treated with calorie restriction and the ketogenic diet. Issues of implementation and use protocols are presented for the metabolic management of brain cancer. This article is part of a Special Issue entitled: Bioenergetics of Cancer. 2010 Published by Elsevier B.V.

Source: EMBASE
65. Innovative therapies for children with cancer pediatric phase I study of erlotinib in brainstem glioma and relapsing/refractory brain tumors


**Citation:** Neuro-Oncology, January 2011, vol./is. 13/1(109-118), 1522-8517;1523-5866 (January 2011)

**Publication Date:** January 2011

**Abstract:** This multicenter phase I study aimed to establish the recommended dose (RD) of the epidermal growth factor receptor (EGFR) inhibitor erlotinib, given as monotherapy or with radiotherapy to children with malignant brain tumors. Group 1 included patients with refractory or relapsing brain tumors receiving erlotinib alone, and group 2 included newly diagnosed patients with brainstem gliomas receiving radiotherapy and erlotinib. A conventional 3 1 3 dose escalation and a continual reassessment method, respectively, were utilized in 4 dose levels: 75, 100, 125, and 150 mg/m$^2$ per day. Fifty-one children were enrolled (30 and 21, respectively); 50 received treatment. The RD of erlotinib was 125 mg/m$^2$ per day as monotherapy or in combination with radiotherapy. Overall, 230 adverse events in 44 patients were possibly treatment related (216, grades 1 and 2; 9, grade 3; 1, grade 4; 4, grade 5). Dermatologic and neurologic symptoms were common; intratumoral hemorrhage was confirmed in 3 patients. In group 1, 8 of 29 patients (28%) had stable disease with tumor regression approaching 50% in a malignant glioma and an anaplastic oligoastrocytoma. In group 2, overall survival was 12.0 months. EGFR overexpression by immunohistochemistry was found in 17 of 38 (45%) tumor samples analyzed, with a partial gain of 7p11.2 in 1 glioblastoma; phosphate and tensin homolog loss was frequent in brainstem glioma (15 of 19). Mean (95% CI) apparent clearance and volume of distribution for erlotinib were 4.0 L/h (3.4-4.5 L/h) and 98.6 L (69.8-127.0 L), respectively, and were independent of the dose level; mean half-life was 16.6 hours. Thus, erlotinib 125 mg/m$^2$ per day has an acceptable tolerability profile in pediatric patients with brain tumors and can be combined with radiotherapy. The Author(s) 2010.

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**Author(s)** Creak A.L., Tree A., Saran F.

**Citation:** Clinical Oncology, April 2011, vol./is. 23/3(189-198), 0936-6555 (April 2011)

**Publication Date:** April 2011

**Abstract:** Aims: Primary brain tumours in adults are rare, with high-grade gliomas (HGG) being the most common and most aggressive type. The clinical management of rare tumours such as HGG can be heterogeneous across different cancer centres. The aim of this survey was to determine current UK practice in the primary management of HGG, particularly in light of the improved outcomes reported recently. Materials and methods: In February 2009, a questionnaire was sent to 71 consultant clinical oncologists in the UK who were reported to have a neuro-oncology practice. Questions focussed on the radiotherapeutic management of HGG. Results: In total, 46/71 (65%) completed questionnaires were returned; 31/46 (67%) routinely used magnetic resonance imaging/computed tomography fusion for radiotherapy planning; 34/36 (94%) routinely prescribed 60 Gy in 30 fractions in a single phase; 7/36 (19%) would consider 54-55 Gy in 30 fractions in selected clinical scenarios; 42/46 (91%) defined the planning target volume (PTV) as the gross tumour volume (GTV) + 2 - 3 cm margin and 42/46 (91%) outlined at least one ‘organ at risk’ (OAR). Accepted tolerance doses varied considerably, e.g. retina range: 30-54. Gy. Sixty-four per cent of clinicians (27/42) compromise the PTV and 30%
the GTV in order to keep OARs within preset tolerances. Nearly one-third (14/42) involve the patient in this decision-making process, e.g. weighing up the risk of late toxicity with the risks of reducing the dose to the PTV. Conclusion: The results of this survey show areas of strong agreement as well as areas of variation in clinical practice of aspects of treatment planning for HGG between UK neuro-oncologists. 2010 The Royal College of Radiologists.

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67. Antiangiogenic combination therapy after local radiotherapy with topotecan radiosensitizer improved quality of life for children with inoperable brainstem gliomas

Author(s) Kivivuori S.-M., Riikonen P., Valanne L., Lonnqvist T., Saarinen-Pihkala U.M.

Citation: Acta Paediatrica, International Journal of Paediatrics, January 2011, vol./is. 100/1(134-138), 0803-5253;1651-2227 (January 2011)

Publication Date: January 2011

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68. A phase II study of metronomic oral topotecan for recurrent childhood brain tumors

Author(s) Minturn J.E., Janss A.J., Fisher P.G., Allen J.C., Patti R., Phillips P.C., Belasco J.B.

Citation: Pediatric Blood and Cancer, January 2011, vol./is. 56/1(39-44), 1545-5009;1545-5017 (January 2011)

Publication Date: January 2011

Abstract: Background: The prognosis for recurrent or refractory brain tumors in children is poor with conventional therapies. Topotecan is a topoisomerase I inhibitor with good central nervous system (CNS) penetration following oral administration. Increased efficacy of topotecan has been demonstrated with prolonged low-dose daily treatment in pre-clinical models. To investigate further this drug delivered orally in pediatric CNS malignancies, a phase II study in children with recurrent or refractory brain tumors was performed.

Procedure: Patients <=21 years of age at diagnosis with a recurrent, progressive, or refractory primary CNS malignancy and measurable disease, were eligible. Patients enrolled into four strata: ependymoma (N = 4), high-grade glioma (HGG) (N = 6), brainstem glioma (BSG) (N = 13), and primitive neuroectodermal tumor (PNET) (N = 8). Oral topotecan was administered once daily at a dose of 0.8 mg/m<sup>2</sup>/day for 21 consecutive days repeated every 28 days. Response and toxicity profiles were evaluated.

Results: Twenty-six patients were evaluable (median age 9.2 years; 10 males). Two objective responses were observed in PNET patients with disseminated tumor at study entry. These two patients remain alive and in remission 7 and 9.5 years off study. Four other patients (two BSG, one PNET, and one HGG) had stable disease (median 4.6 months). The most common toxicities were hematologic. Conclusions: Daily oral topotecan at a dose of 0.8 mg/m<sup>2</sup>/day can be safely administered to children with recurrent or refractory brain tumors. This regimen identified activity in recurrent PNET. The prolonged progression free survival (PFS) in two PNET patients justifies consideration of this regimen in more advanced clinical trials. 2010 Wiley-Liss, Inc.

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69. Lack of efficacy of bevacizumab plus irinotecan in children with recurrent malignant glioma and diffuse brainstem glioma: a Pediatric Brain Tumor Consortium study


Citation: Journal of clinical oncology : official journal of the American Society of Clinical Oncology, June 2010, vol./is. 28/18 (3069-3075), 1527-7755 (20 Jun 2010)

Publication Date: June 2010

Abstract: PURPOSE: A phase II study of bevacizumab (BVZ) plus irinotecan (CPT-11) was conducted in children with recurrent malignant glioma (MG) and intrinsic brainstem glioma (BSG). PATIENTS AND METHODS: Eligible patients received two doses of BVZ intravenously (10 mg/kg) 2 weeks apart and then BVZ plus CPT-11 every 2 weeks until progressive disease, unacceptable toxicity, or a maximum of 2 years of therapy. Correlative studies included diffusion weighted and T1 dynamic contrast-enhanced permeability imaging, BVZ pharmacokinetics, and estimation of vascular endothelial growth factor receptor 2 (VEGFR-2) phosphorylation in peripheral blood mononuclear cells (PBMC) after single-agent BVZ. RESULTS: Thirty-one evaluable patients received a median of two courses of BVZ plus CPT-11 (range, 1 to 19). No sustained responses were observed in either stratum. Median time to progression for all 34 eligible patients enrolled was 127 days for MG and 71 days for BSG. Progression-free survival rates at 6 months were 41.8% and 9.7% for MG and BSG, respectively. Toxicities related to BVZ included grade 1 to 3 fatigue in seven patients, grade 1 to 2 hypertension in seven patients, grade 1 CNS hemorrhage in four patients, and grade 4 CNS ischemia in two patients. The mean diffusion ratio decreased after two doses of BVZ in patients with MG only. Vascular permeability parameters did not change significantly after therapy in either stratum. Inhibition of VEGFR-2 phosphorylation in PBMC was detected in eight of 11 patients after BVZ exposure. CONCLUSION: BVZ plus CPT-11 was well-tolerated but had minimal efficacy in children with recurrent malignant glioma and brainstem glioma.

Source: EMBASE

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70. A phase II trial and pharmacokinetic study of oxaliplatin in children with refractory solid tumors: A Children's Oncology Group study


Citation: Pediatric Blood and Cancer, September 2010, vol./is. 55/3 (440-445), 1545-5009;1545-5017 (September 2010)

Publication Date: September 2010

Abstract: Background. Platinating agents are used in the treatment of a spectrum of childhood cancers. Oxaliplatin, a third generation platinum compound, may provide less toxicity and be more effective. A phase 2 study was performed to estimate the response rate to single agent oxaliplatin in patients with refractory pediatric solid tumors, and to further describe the toxicities and pharmacokinetics of the drug in this population. Patients and Methods. Subjects, <=21 years of age at original diagnosis, received oxaliplatin (130 mg/m<sup>2</sup> <sup>+</sup><sub>2</sub>-<sup>+</sup>) intravenously every 21 days. Prior platinum exposure was acceptable. Histologies included: Ewing sarcoma/ peripheral PNET, osteosarcoma, rhabdomyosarcoma, neuroblastoma, high and low grade astrocytoma, brain stem glioma, ependymoma, hepatoblastoma and selected rare tumors. A two-stage design, enrolling 10+10 subjects, was used for each disease stratum. Limited sampling pharmacokinetic studies were performed. Results. Of 124 eligible subjects (75 males), 113 were evaluable for response and 69 (62%) had received platinum previously. Only one objective response was observed, a partial response in a 6-year-old child with ependymoma. An additional 13 subjects with various other solid tumors had stable disease, receiving a median (range) of 13.5 (2-17) cycles. Five subjects completed 17 treatment cycles. Thrombocytopenia was the most common toxicity observed. The median (range) terminal half-life and clearance for
ultrafiltrable platinum were 293 (187-662 hr) and 14.0 (1.9-24.9 L/hr/m^2), respectively (n=49). Conclusions. Although reasonably well tolerated, oxaliplatin administered as a single agent has limited activity in pediatric patients with relapsed or refractory solid tumors. 2010 Wiley-Liss, Inc.

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71. A phase i and biology study of gefitinib and radiation in children with newly diagnosed brain stem gliomas or supratentorial malignant gliomas


**Citation:** European Journal of Cancer, December 2010, vol./is. 46/18(3287-3293), 0959-8049 (December 2010)

**Publication Date:** December 2010

**Abstract:** Purpose: To estimate the maximum-tolerated dose (MTD); study the pharmacology of escalating doses of gefitinib combined with radiation therapy in patients <=21 years with newly diagnosed intrinsic brainstem gliomas (BSG) and incompletely resected supratentorial malignant gliomas (STMG); and to investigate epidermal growth factor receptor (EGFR) amplification and expression in STMG. Patients and methods: Three strata were identified: stratum 1A - BSG; stratum 1B - incompletely resected STMG not receiving enzyme-inducing anticonvulsant drugs (EIACD); and stratum II - incompletely resected STMG receiving EIACD. Dose escalation using a modified 3 + 3 cohort design was performed in strata IA and II. The initial gefitinib dosage was 100 mg/m^2/d commencing with radiation therapy and the dose-finding period extended until 2 weeks post-radiation. Pharmacokinetics (PK) and biology studies were performed in consenting patients. Results: Of the 23 eligible patients, 20 were evaluable for dose-finding. MTDs for strata IA and II were not established as accrual was halted due to four patients experiencing symptomatic intratumoral haemorrhage (ITH); two during and two post dose-finding. ITH was observed in 0 of 11 patients treated at 100 mg/m^2/d, 1 of 10 at 250 mg/m^2/d and 3 of 12 at 375 mg/m^2/d. Subsequently a second patient at 250 mg/m^2/d experienced ITH. PK analysis showed that the median gefitinib systemic exposure increased with dosage (p = 0.04). EGFR was over-expressed in 5 of 11 STMG and amplified in 4 (36%) samples. Conclusion: This trial provides clear evidence of EGFR amplification in a significant proportion of paediatric STMG and 250 mg/m^2/d was selected for the phase II trial. 2010 Elsevier Ltd. All rights reserved.

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72. A multi-centre Canadian pilot study of metronomic temozolomide combined with radiotherapy for newly diagnosed paediatric brainstem glioma


**Citation:** European Journal of Cancer, December 2010, vol./is. 46/18(3271-3279), 0959-8049 (December 2010)

**Publication Date:** December 2010

**Abstract:** Purpose: Survival rates for paediatric diffuse intrinsic brainstem glioma (DIBSG) are dismal. Metronomic dosing of temozolomide (TMZ) combined with standard radiotherapy may improve survival by increasing the therapeutic index and anti-angiogenic effect of TMZ. This study aimed to evaluate the safety and efficacy of this regimen in...
paediatric DIBSG patients. Methods: Children aged 18 years or younger with newly diagnosed DIBSG were treated with standard radiotherapy and concomitant metronomic TMZ at 85 mg/m²/day for 6 weeks, followed by metronomic TMZ monotherapy at the same dose. Treatment was continued until tumour progression or unacceptable toxicity occurred. Primary endpoints included overall survival and toxicities. For patients who consented, plasma and urine samples were collected at diagnosis, post-induction and prior to each course of maintenance therapy for the quantification of angiogenesis markers. Results: Fifteen eligible patients were enrolled, with a median age of 6.4 years. The most common toxicities were myelosuppression, most notably prolonged lymphopaenia and thrombocytopaenia. The only dose-limiting toxicity was thrombocytopaenia. Intratumoural haemorrhage was confirmed in one patient. Median time to progression was 5.13 months (95% CI = 6.4, 10.8) and median overall survival (OS) was 9.8 months (95% CI = 6.4, 10.8). Six-months OS was 80% +/- 10.3%, with a 1-year OS of 20% +/- 10.3%. Serum levels of both VEGF and endoglin tended to decrease during the first two cycles of therapy. Conclusion: Chemoradiotherapy with metronomic dosing of TMZ showed similar toxicity to previous TMZ regimens, and does not appear to improve survival in paediatric DIBSG. 2010 Elsevier Ltd. All rights reserved.

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73. Role of temozolomide in the treatment of newly diagnosed diffuse brainstem glioma in children: Experience at a single institution

Author(s) Chiang K.-L., Chang K.-P., Lee Y.-Y., Huang P.-I., Hsu T.-R., Chen Y.-W., Chang F.-C., Wong T.-T.

Citation: Child's Nervous System, August 2010, vol./is. 26/8(1035-1041), 0256-7040 (August 2010)

Publication Date: August 2010

Abstract: Purpose: The purpose of this study was to assess the efficacy of TMZ on diffuse brainstem glioma, either concomitant with radiotherapy or as an adjuvant treatment after radiotherapy in children. Methods and materials: Eighteen children (median age at diagnosis was 8.3 years) meet the following criteria: (1) newly diagnosed diffuse brainstem glioma; (2) aged less than 18 years old, which were treated with TMZ at Taipei Veterans General Hospital from January 2004 to December 2008. They were divided into two groups according to treatment modalities: a radiotherapy alone followed by adjuvant TMZ (RT+TMZ) group received conventional radiation after initial diagnosis, and a concomitant chemoradiotherapy followed by adjuvant TMZ (CCRT+TMZ) group received concurrent chemotherapy during radiation with TMZ (75 mg/M2/day). After completion of the radiotherapy, TMZ (150 mg/M2) was administered once per day for five consecutive days for all enrolled patients in each 28-day cycle. We evaluated the progression-free survival in both groups of patients. Results: There were 10 patients in RT+TMZ group and eight in CCRT+TMZ group. All patients experienced progression of disease. Twelve patients (75%) died, and all deaths were attributed to the disease progression. The median progression-free survival (PFS) was 7.4 months for the RT+TMZ group and 6.4 months for the CCRT+TMZ group. The 6-month and 1-year PFS in the RT+TMZ group were 70% (SD 14%) and 30% (SD 14%), respectively, and in the CCRT+TMZ group, they were 50% (SD 17%) and 0%, respectively. The log-rank test in PFS between the two groups was not statistically significant. Conclusions: In this study, CCRT with TMZ followed by adjuvant TMZ did not result in a better outcome when compared with RT alone followed by adjuvant TMZ. In addition, TMZ either as adjuvant therapy or as CCRT did not improve the prognosis of the patients with newly diagnosed diffuse brainstem glioma. 2010 Springer-Verlag.

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74. Convection-enhanced delivery of nanoliposomal CPT-11 (Irinotecan) in human brainstem glioma xenografts

Author(s) Hashizume R., Aoki Y., Serwer L.P., Drummond D., Noble C., Park J., Bankiewicz K., James D.C., Gupta N.

Citation: Neuro-Oncology, November 2010, vol./is. 12/(iv87-iv88), 1522-1517 (November 2010)

Publication Date: November 2010

Abstract: Most children with infiltrative brainstem gliomas die within 2 years after initial diagnosis. These tumors are not amenable to surgical resection, and the blood-brain barrier (BBB) limits the distribution of systemically administered agents. The development of new therapeutic approaches circumventing the BBB is generally considered important to improving outcomes for brainstem glioma patients. Convection-enhanced delivery (CED) uses positive pressure infusion for drug administration into the brain parenchyma and has demonstrated promising results in both animal models and clinical trials. This technique is well suited for the delivery of liposomes and particulate drug carriers, which have the potential to reach cellular targets with improved specificity. In the current study, we treated rats bearing brainstem glioma xenografts with nanoparticle liposomes containing CPT-11 (nanoliposomal CPT-11) by CED. In naive rats, lacking intracranial xenograft, no systemic toxicity, such as weight loss or diarrhea, was observed with doses of 0.25, 0.5, and 1.0 mg/kg CPT-11. To determine the in vivo distribution of nanoliposomal CPT-11, hydrophobic fluorophore (DiI)-labeled nanoliposomal CPT-11 was administered into rat brainstems by CED. Using fluorescence optical imaging, a detectable fluorescence signal was evident in the brainstem 6 hours following liposomal administration, with the detectable signal persisting for more than 14 days. In a therapy-response experiment, athymic rats bearing luciferase-modified human GS2 glioblastoma tumors in the right pontine tegmentum were randomized to nanoliposomal treatment groups with treatments consisting of empty nanoliposomes, 0.01, 0.1, or 1.0 mg/kg nanoliposomal CPT-11 delivered by CED. Treatment with 1.0 mg of nanoliposomal CPT-11 significantly inhibited tumor growth compared with control nanoliposomes as well as lower doses of nanoliposomal CPT-11. These results support anatomically correct modeling of brainstem glioma for evaluating novel therapies and therapeutic delivery approaches.

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75. Therapeutic efficacy and safety of TRAIL-producing human adipose tissue-derived mesenchymal stem cells against experimental brainstem glioma


Citation: Child's Nervous System, October 2010, vol./is. 26/10(1460), 0256-7040 (October 2010)

Publication Date: October 2010

Abstract: Mesenchymal stem cells (MSCs) have an extensive migratory capacity for gliomas, which is comparable to that of neural stem cells. Among the various types of MSCs, human adipose tissue-derived MSCs (hATMSC) emerge as one of the most attractive vehicles for gene therapy because of their high throughput, lack of ethical concerns, and availability and ease of isolation. We evaluated the therapeutic potential and safety of genetically engineered hAT-MSCs encoding the tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) against brainstem gliomas. hAT-MSCs were isolated from human fat tissue, characterized, and transfected with TRAIL using nucleofector. The therapeutic potential of TRAIL-producing hAT-MSCs (hAT-MSC.TRAIL) was confirmed...
using in vitro and in vivo studies. The final fate of injected hAT-MSCs was traced in long-survival animals. The characterization of hAT-MSCs revealed the expression of MSC specific cell-type markers and their differentiation potential into neuronal lineage. Short-term outcomes included a 56.3% reduction of tumor volume (P<0.001) with increased apoptosis (3.03-fold, P<0.05) in animals treated with hAT-MSC.TRAIL compared with the control groups. Long-term outcomes included a significant survival benefit in the hAT-MSC.TRAIL-treated group (26 days of median survival in the control group vs 84 days in the hAT-MSC.TRAIL-treated group, P< 0.0001), without any evidence of mesenchymal differentiation in vivo. Our study demonstrated the therapeutic efficacy and safety of nonvirally engineered hAT-MSCs against brainstem gliomas.

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76. Phase I/II study of vandetanib for patients with recurrent malignant gliomas

Author(s) McNicol K.A., Kreisl T.N., Iwamoto F.M., Sul J., Fine H.A.

Citation: Journal of Clinical Oncology, May 2010, vol./is. 28/15 SUPPL. 1, 0732-183X (20 May 2010)

Publication Date: May 2010

Abstract: Background: EGFR and VEGFR signaling have been implicated in the development and growth of glioblastoma, and simultaneous inhibition of both of these signal transduction pathways has the potential to be a more effective therapeutic approach than inhibiting a single pathway. Vandetanib is an inhibitor of VEGFR-2 and EGFR tyrosine kinase activities, which has previously been shown to have anti-tumor activity in histologically diverse pre-clinical models of human cancer, including subcutaneous and orthotopic models of human glioma. Methods: A phase I study evaluated the MTD of vandetanib in patients on enzyme-inducing antiepileptics (EIAEDs). Eligibility criteria were histologically proven glioblastoma (GBM), anaplastic glioma (AG), progressive low-grade glioma (LGG), or radiographically diagnosed brainstem gliomas, radiologic progression after RT, age >=18, KPS >=60, and adequate bone marrow and organ function. There was no limit on the number of prior relapses or chemotherapies. Doses were escalated on a 3 + 3 design, with dose levels of 300, 400, 500, 700, and 900 mg QD. MTD was defined as the highest dose with DLTs in 1/6 or fewer patients. In phase II, patients with histologically proven AG were eligible, with other eligibility criteria as outlined above. Patients on EIAEDs were excluded from the phase II study. Patients received vandetanib 300 mg QD on 4-week cycles. Primary endpoint was PFS6. Results: In phase I, 15 patients were evaluated (8 GBM; 5 AG, 2 LGG). Median age 44 (18-66); median KPS 90 (80-100); median prior chemotherapies 1 (1-5). The MTD was determined to be 400 mg. There was 1/6 DLT (grade 3 rash) at this dose. At 500 mg there were 2/6 DLTs; one grade 3 prolonged QTc, and one grade 4 DVT/PE. In the phase II trial, there were 32 patients with AG. Median age 41 (18-69), median KPS 90 (60-100), median prior chemotherapies 2 (0-6). There were 2 PRs, and 13 SDs. One patient remains progression-free on study for over 21 months. PFS6 was 13.2% (95% CI: 4.2-27.5%), and median PFS was 1.8 mo (95% CI: 0.89-2.66 mo). Median OS was 7.4 mo (95% CI: 3.9-12.5 mo). Conclusions: Vandetanib is well tolerated, with a MTD of 400 mg QD in patients taking EIAEDs. In patients not on EIAEDs, vandetanib 300 mg QD had only limited monotherapy activity in recurrent AG.

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77. Nimotuzumab in pediatric glioma

Author(s) Lam C., Bouffet E., Bartels U.

Citation: Future oncology (London, England), November 2009, vol./is. 5/9(1349-1361), 1744-8301 (Nov 2009)
Abstract: High-grade gliomas and diffuse brainstem gliomas carry a very poor prognosis despite current therapies, and account together for the largest number of deaths in children with brain tumors. Many of these tumors have been found to overexpress the EGFR receptor (EGFR). Nimotuzumab (h-R3) is a humanized monoclonal antibody against the EGFR, and consequently inhibits tyrosine kinase activation. In vitro and in vivo studies have supported the antiproliferative, antiangiogenic, pro-apoptotic and radiosensitizing activities of nimotuzumab. Emerging trials suggest a promising role for nimotuzumab as a therapeutic agent in patients with high-grade gliomas. This review attempts to provide a context for the evolving interest and evidence for nimotuzumab in pediatric glioma.

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78. A literature review of the recent radiotherapy clinical trials in pediatric brain tumors

Author(s) Skowronska-Gardas A.

Citation: Reviews on recent clinical trials, January 2009, vol./is. 4/1(42-55), 1574-8871 (Jan 2009)

Abstract: Primary central nervous system neoplasms are the second malignancy in children following leukemia. Despite developments in neurosurgery and new drugs in chemotherapy, irradiation is an essential part of the management in most of pediatric brain tumors. A good treatment strategy should consider not only survival but also the quality of life. The new approach of radiotherapy and importance of new drugs in combined treatment are recently considered. This article summarizes the recent clinical trials conducted in pediatric brain tumors management. Results of randomized study of pre-irradiation chemotherapy versus radiotherapy alone for medulloblastoma were presented by SIOP/UKCCSG PNET-3. The French M-SFOP 98 protocol considered hyper-fractionated radiotherapy with reduced boost volume, without chemotherapy and estimated impact on early relapses and intellectual function. The influence of radiotherapy quality on survival in high-risk medulloblastoma patients was evaluated in POG Trial 9031. In the treatment of low-grade glioma in children the effectiveness of novel combination chemotherapy was considered. Role of new drugs as temozolomid, topotecan and RMP-7 was investigated in pediatric high grade glioma and brain stem tumors. Impact of combined treatment on outcome of intracranial germ-cell tumors was investigated as well.

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79. Pediatric gliomas

Author(s) Pfister S., Witt O.

Citation: Gliomas, 2009, vol./is. 171/(67-81), 0080-0015 (2009)

Abstract: Pediatric gliomas comprise a clinically, histologically, and molecularly very heterogeneous group of CNS tumors. In addition, these tumors are largely different from their counterparts occurring in adults, although they are histologically indistinguishable and uniformly classified by the current WHO classification for CNS tumors. Pilocytic astrocytoma (WHO grade I), mainly arising in the posterior fossa, is the most common representative in children, whereas glioblastoma multiforme (WHO grade IV) predominates in adults. When radical surgical resection is possible in low-grade gliomas, it will likely cure the patient. If complete surgical resection is not possible, however, for example in brainstem gliomas, which are defined by their anatomic localization rather than by their histological or molecular features, therapeutic options are limited and prognosis is usually
Recent genome-wide analyses applying different microarray-based methods to investigate DNA copy-number aberrations, mRNA expression signatures, and methylation patterns have shed some light on the pathways involved in the pathogenesis of pediatric gliomas. Mitogen-activated protein kinase (MAPK) and PI3K/AKT signaling were identified as prominent oncogenic pathways in astrocytic tumors in several studies, whereas NOTCH signaling was implicated in the pathogenesis of a subset of intracranial ependymomas. Future therapeutic strategies targeting these (and other) pathways or conferring epigenetic modifications in the tumor might contribute to a better treatment outcome of patients with unresectable or disseminated tumors at diagnosis. Consideration of reliable molecular markers for outcome prediction will most likely result in a better stratification of patients into different risk groups with adjusted treatment intensity in the future. 2009 Springer Berlin Heidelberg.

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80. Role of surgery in brainstem gliomas

Author(s) Mohanty A.

Citation: Neurology India, July 2009, vol./is. 57/3(231-232), 0028-3886;1998-4022 (01 Jul 2009)

Publication Date: July 2009

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81. Long-term outcome of high-precision radiotherapy in patients with brain stem gliomas: Results from a difficult-to-treat patient population using fractionated stereotactic radiotherapy

Author(s) Combs S.E., Steck I., Schulz-Ertner D., Welzel T., Kulozik A.E., Behnisch W., Huber P.E., Debus J.

Citation: Radiotherapy and Oncology, April 2009, vol./is. 91/1(60-66), 0167-8140 (April 2009)

Publication Date: April 2009

Abstract: Introduction: To assess long-term outcome in 85 patients with brain stem gliomas treated with fractionated stereotactic radiation therapy (FSRT). Patient and methods: Thirty-nine patients were females, and 46 were males. Median age at primary diagnosis was 26 years. Thirty-one patients were younger than 18 years. Histopathological examination confirmed a low-grade glioma in 57 patients. Of the group of high-grade gliomas, six were anaplastic astrocytomas, and two were classified as glioblastoma. Radiation therapy was performed as FSRT. The median target volume was 101 ml. We applied a median dose of 54 Gy in conventional fractionation of 1.8 Gy. In seven of 85 patients (8%) FSRT was performed as re-irradiation. Results: The median follow-up time was 42 months. Median overall survival (OS) was 81 months. OS rates were 77% at 12 months, 70% at 24 months, and 63% at 36 months. Significant impact on OS could be shown for pilocytic histology, age, neurosurgical resection as well as for the presence of cyst on MR-imaging. Median progression-free survival (PFS) after FSRT was 52 months. PFS rates at 12 months were 70%, and 63% and 58% at 24 and 36 months, respectively. Histology, partial neurosurgical resection and the duration of symptoms could be identified as significant prognostic factors. Conclusion: Long-term outcome of FSRT in patients with brain stem gliomas is acceptable with low rates of side effects. Significant impact on outcome could be shown for histology, age, extent of neurosurgical resection as well as for cyst formation. No dose-response relationship could be observed. 2009 Elsevier Ireland Ltd. All rights reserved.
82. Delayed toxicity from gamma knife radiosurgery to lesions in and adjacent to the brainstem

Author(s) Davidson L., Zada G., Yu C., Petrovich Z., Pagnini P.G., Zee C.-S., Giannotta S.L., Zelman V., Apuzzo M.L.J.

Citation: Journal of Clinical Neuroscience, September 2009, vol./is. 16/9(1139-1147), 0967-5868 (September 2009)

Publication Date: September 2009

Abstract: The aims of this study were to assess the incidence of, and risk factors for, delayed toxicity following gamma knife stereotactic radiosurgery (GKRS) to lesions in and adjacent to the brainstem. We retrospectively evaluated the delayed toxicity of GKRS following the treatment of 114 lesions in and adjacent to the brainstem in 107 patients. The median tumor volume was 6.2 cm³ and the median dose to the tumor margin was 16 Gy. The mean follow-up was 40 months. Thirteen patients (12%) demonstrated clinical evidence of delayed toxicity, with a median latency to the development of toxicity of 6 months. The actuarial incidence of toxicity at 1 year and 5 years was 10.2% and 13.8%. Larger tumor volume (p = 0.02) and larger treatment volume (p = 0.04) were associated with an increased incidence of delayed toxicity. Large lesions adjacent to the brainstem have a higher than previously suspected rate of delayed toxicity. 2009 Elsevier Ltd. All rights reserved.

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83. The Role of Hypofractionation Radiotherapy for Diffuse Intrinsic Brainstem Glioma in Children: A Pilot Study


Citation: International Journal of Radiation Oncology Biology Physics, March 2009, vol./is. 73/3(722-726), 0360-3016 (01 Mar 2009)

Publication Date: March 2009

Abstract: Purpose: Most children with a diffuse intrinsic brainstem glioma will die within 1 year after diagnosis. To reduce patient burden, we investigated the feasibility of a radical hypofractionation radiotherapy schedule, given over 3 weeks, as an alternative to the standard regimen (30 fractions over 6 weeks). Methods and Materials: Nine children, ages 3-13, were treated by 13 fractions of 3 Gy (n = 8) or 6 fractions of 5.5 Gy (n = 1) given over 3 weeks. All patients had symptoms for <=3 months and >=2 signs of the neurologic triad (long tract signs, ataxia, cranial nerve deficit). Bilateral involvement of the pons (n = 8), encasement of the basilar artery (n = 7) and extension into the cerebellar peduncle (n = 6) was visible on magnetic resonance imaging. Results: Symptom improvement occurred in all patients within 2 weeks after start of radiotherapy. At a mean follow-up time of 15 months, 7 patients have died. Median time to progression and overall survival was 4.9 and 8.6 months, respectively. Median time to death after progression was 3.6 months. No Grade 3 or 4 toxicity was observed. In a recently published review of clinical trials, median time to progression, overall survival, and time between progression and death ranged from 5.0-8.8, 7.0-16, and 1.0-4.5 months, respectively, with more aggressive regimens. Conclusion: This radical hypofractionation radiotherapy regimen for children with diffuse intrinsic brainstem glioma is feasible and associated with no Grade 3 or 4 toxicities. With a minimal overall treatment time, it offers quick symptom relief and outcome results within the range of published data. 2009 Elsevier Inc. All rights reserved.

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84. Motexafin gadolinium and involved field radiation therapy for intrinsic pontine glioma of childhood: a Children's Oncology Group phase I study


Citation: Neuro-oncology, October 2008, vol./is. 10/5(752-758), 1522-8517 (Oct 2008)

Publication Date: October 2008

Abstract: The purpose of this study was to determine the dose-limiting toxicities, maximum tolerated dose, pharmacokinetics, and intratumor and brain distribution of motexafin gadolinium (MGd) with involved field radiation therapy in children with newly diagnosed intrinsic pontine gliomas. MGd was administered as a 5-min intravenous bolus 2-5 h prior to standard radiation. The starting dose was 1.7 mg/kg. After first establishing that 5 doses/week for 6 weeks was tolerable, the dose of MGd was escalated until dose-limiting toxicity was reached. Radiation therapy was administered to 54 Gy in 30 once-daily fractions. Forty-four children received MGd at doses of 1.7 to 9.2 mg/kg daily prior to radiation therapy for 6 weeks. The maximum tolerated dose was 4.4 mg/kg. The primary dose-limiting toxicities were grade 3 and 4 hypertension and elevations in serum transaminases. Median elimination half-life and clearance values were 6.6 h and 25.4 ml/kg/h, respectively. The estimated median survival was 313 days (95% confidence interval, 248-389 days). The maximum tolerated dose of MGd and the recommended phase II dose was 4.4 mg/kg when administered as a daily intravenous bolus in conjunction with 6 weeks of involved field radiation therapy for pediatric intrinsic pontine gliomas.

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85. Preradiation chemotherapy may improve survival in pediatric diffuse intrinsic brainstem gliomas: final results of BSG 98 prospective trial

Author(s) Frappaz D., Schell M., Thiesse P., Marec-Berard P., Mottolese C., Perol D., Bergeron C., Philip T., Ricci A.C., Galand-Desme S., Szathmari A., Carrie C.

Citation: Neuro-oncology, August 2008, vol./is. 10/4(599-607), 1522-8517 (Aug 2008)

Publication Date: August 2008

Abstract: Radiation therapy remains the only treatment that provides clinical benefit to children with diffuse brainstem tumors. Their median survival, however, rarely exceeds 9 months. The authors report a prospective trial of frontline chemotherapy aimed at delaying radiation until time of clinical progression. The aim was to investigate the possibility that radiotherapy would maintain its activity in children whose disease progressed after chemotherapy. Twenty-three patients took part in this protocol, the BSG 98 protocol, which consisted of frontline chemotherapy alternating hematotoxic and nonhematotoxic schedules. Each cycle included three courses delivered monthly; the first course was 1,3-bis(2-chloroethyl)-1-nitrosoureasiplatin, and the second and third were high-dose methotrexate. Three patients underwent one cycle; 5 patients each, two and three cycles; and 10 patients, four cycles. Twenty of the 23 patients eventually received local radiation therapy. A historical cohort of 14 patients who received at least local radiation therapy served as controls. Four patients experienced severe iatrogenic infections, and 11 patients required platelet transfusions. Median survival increased significantly in patients participating in the protocol compared to that in the historical controls (17 months, 95% confidence interval [CI], 10-23 months, vs. 9 months, 95% CI, 8-10 months; p = 0.022), though hospitalization was prolonged (57 vs. 25 days, p = 0.001). Although frontline chemotherapy alternating hematotoxic and nonhematotoxic schedules significantly increases overall median survival, its cost from infection and hospitalization deserves
honest discussion with the children and their parents.

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86. Concurrent radiotherapy with temozolomide followed by adjuvant temozolomide and cis-retinoic acid in children with diffuse intrinsic pontine glioma

Author(s) Sirachainan N., Pakakasama S., Visudithbhan A., Chiamchanya S., Tuntiyatorn L., Dhanachai M., Laothamatas J., Hongeng S.

Citation: Neuro-oncology, August 2008, vol./is. 10/4(577-582), 1522-8517 (Aug 2008)
Publication Date: August 2008
Abstract: The prognosis of children with diffuse intrinsic pontine glioma (DIPG) is very poor. Radiotherapy remains the standard treatment for these patients, but the median survival time is only 9 months. Currently, the use of concurrent radiotherapy with temozolomide (TMZ) has become the standard care for adult patients with malignant gliomas. We therefore investigated this approach in 12 children diagnosed with DIPG. The treatment protocol consisted of concurrent radiotherapy at a dose of 55.8-59.4 Gy at the tumor site with TMZ (75 mg/m(2)/day) for 6 weeks followed by TMZ (200 mg/m(2)/day) for 5 days with cis-retinoic acid (100 mg/m(2)/day) for 21 days with a 28-day cycle after concurrent radiotherapy. Ten of the 12 patients had a clinical response after the completion of concurrent radiotherapy. Seven patients had a partial response, four had stable disease, and one had progressive disease. At the time of the report, 9 of the 12 patients had died of tumor progression, one patient was alive with tumor progression, and two patients were alive with continuous partial response and clinical improvement. The median time to progression was 10.2 +/- 3.0 months (95% confidence interval [CI], 4.2-16.1 months). One-year progression-free survival was 41.7% +/- 14.2%. The median survival time was 13.5 +/- 3.6 months (95% CI, 6.4-20.5 months). One-year overall survival was 58% +/- 14.2%. The patients who had a partial response after completion of concurrent radiotherapy had a longer survival time (p = 0.036) than did the other patients (those with stable or progressive disease). We conclude that the regimen of concurrent radiotherapy and TMZ should be considered for further investigation in a larger series of patients.

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87. Phase i trial of tipifarnib in children with newly diagnosed intrinsic diffuse brainstem glioma

Author(s) Haas-Kogan D.A., Banerjee A., Kocak M., Prados M.D., Geyer J.R., Fouladi M., McKnight T., Poussaint T.Y., Broniscer A., Blaney S.M., Boyett J.M., Kun L.E.

Citation: Neuro-Oncology, June 2008, vol./is. 10/3(341-347), 1522-8517;1523-5866 (June 2008)
Publication Date: June 2008
Abstract: The purpose of this study is to estimate the maximum-tolerated dose (MTD) and describe toxicities and preliminary clinical effects of tipifarnib, a farnesyltransferase (FTase) inhibitor, administered concurrently with radiation therapy in children with newly diagnosed intrinsic diffuse brainstem glioma (BSG). Children >=3 and <=21 years of age with newly diagnosed nondisseminated intrinsic diffuse BSG were treated with concurrent tipifarnib and radiation, followed by adjuvant tipifarnib. Escalating doses of tipifarnib were administered orally twice daily, continuously, for the entire duration of radiation, followed by
a 2-week break. Postradiation tipifarnib, 200 mg/m<sup>2</sup>/dose, was administered twice daily for 21 consecutive days, in 28-day cycles. Seventeen patients, median age 5.9 years (range, 3.6-13.8), received external beam radiation therapy administered concurrently with tipifarnib at dose levels ranging from 100 to 150 mg/m<sup>2</sup>/dose, followed by adjuvant tipifarnib for up to 24 months in the absence of tumor progression or unacceptable toxicity. Dose-limiting toxicities were grade 3 skin rash in one patient at the 125 mg/m<sup>2</sup>/dose level and two patients at the 150 mg/m<sup>2</sup>/dose level, and grade 3 pneumonia with a normal absolute neutrophil count (ANC) in one patient at the 150 mg/m<sup>2</sup>/dose level. One patient had isolated grade 4 neutropenia at the 150 mg/m<sup>2</sup>/dose level. The MTD of tipifarnib administered was estimated as 125 mg/m<sup>2</sup>/dose b.i.d. When administered concurrently with radiation, the dose-limiting toxicities of tipifarnib are rash, infection with normal ANC, and neutropenia. The MTD of tipifarnib with concurrent radiation is 125 mg/m<sup>2</sup>/dose b.i.d. One-year survival and progression-free survival estimates are 36.4% (SE 16.7%) and 9.4% (SE 6.3%), respectively. Copyright 2008 by the Society for Neuro-Oncology.

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88. Concurrent carbogen and radiation therapy in children with high-risk brainstem gliomas

Author(s) Aquino-Parsons C., Hukin J., Green A.

Citation: Pediatric Blood and Cancer, February 2008, vol./is. 50/2(397-399), 1545-5009;1545-5017 (February 2008)

Publication Date: February 2008

Abstract: In an attempt to improve local control, we assessed the feasibility of the addition of 4 min of carbogen inhalation (as a radiosensitizer) to daily fractionated radiotherapy in pediatric patients with high grade and/or diffuse brainstem gliomas. Ten patients inhaled carbogen for >90% of the radiation treatments. Median survival time from start of therapy was 0.80 years. Carbogen inhalation did not appear to improve the dismal prognosis. 2006 Wiley-Liss, Inc.

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89. Intensity modulated radiation therapy versus three-dimensional conformal radiation therapy for the treatment of high grade glioma: A dosimetric comparison

Author(s) MacDonald S.M., Ahmad S., Kachris S., Vogds B.J., DeRouen M., Gittleman A.E., DeWyngaert K., Vlachaki M.T.

Citation: Journal of Applied Clinical Medical Physics, 2007, vol./is. 8/2(47-60), 1526-9914 (2007)

Publication Date: 2007

Abstract: The present study compared the dosimetry of intensity-modulated radiation therapy (IMRT) and three-dimensional conformal radiation therapy (3D-CRT) techniques in patients treated for high-grade glioma. A total of 20 patients underwent computed tomography treatment planning in conjunction with magnetic resonance imaging fusion. Prescription dose and normal-tissue constraints were identical for the 3D-CRT and IMRT plans. The prescribed dose was 59.4 Gy delivered at 1.8 Gy per fraction using 4 - 10 MV photons. Normal-tissue dose constraints were 50 - 54 Gy for the optic chiasm and nerves, and 55 - 60 Gy for the brainstem. The IMRT plan yielded superior target coverage as compared with the 3D-CRT plan. Specifically, minimum and mean planning target volume
cone down doses were 54.52 Gy and 61.74 Gy for IMRT and 50.56 Gy and 60.06 Gy for 3D-CRT (p <= 0.01). The IMRT plan reduced the percent volume of brainstem receiving a dose greater than 45 Gy by 31% (p = 0.004) and the percent volume of brain receiving a dose greater than 18 Gy, 24 Gy, and 45 Gy by 10% (p = 0.059), 14% (p = 0.015), and 40% (p <= 0.0001) respectively. With IMRT, the percent volume of optic chiasm receiving more than 45 Gy was also reduced by 30.40% (p = 0.047). As compared with 3D-CRT, IMRT significantly increased the tumor control probability (p <= 0.005) and lowered the normal-tissue complication probability for brain and brainstem (p < 0.033). Intensity-modulated radiation therapy improved target coverage and reduced radiation dose to the brain, brainstem, and optic chiasm. With the availability of new cancer imaging tools and more effective systemic agents, IMRT may be used to intensify tumor doses while minimizing toxicity, therefore potentially improving outcomes in patients with high-grade glioma. 2007 Am. Coll. Med. Phys.

Source: EMBASE

90. Phase I trial of single-dose temozolomide and continuous administration of O6-benzylguanine in children with brain tumors: A pediatric brain tumor consortium report

Author(s) Broniscer A., Gururanga S., MacDonald T.J., Goldman S., Packer R.J., Stewart C.F., Wallace D., Danks M.K., Friedman H.S., Poussaint T.Y., Kun L.E., Boyett J.M., Gajjar A.

Citation: Clinical Cancer Research, November 2007, vol./is. 13/22(6712-6718), 1078-0432 (15 Nov 2007)

Publication Date: November 2007

Abstract: Purpose: To estimate the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) of escalating doses of temozolomide combined with O<sup>6</sup>-benzylguanine in patients <= 21 years with recurrent brain tumors. Experimental Design: Treatment strata consisted of patients who had previously received no or local radiotherapy (Str1) and patients who had undergone craniospinal radiotherapy or myeloablative chemotherapy (Str2). One-hour i.v. administration of O<sup>6</sup>-benzylguanine at 120 mg/m<sup>2</sup> was followed by 48-h continuous infusion at 30 mg/m<sup>2</sup> bolus. Single-dose temozolomide at five dosage levels (267, 355, 472, 628, and 835 mg/m<sup>2</sup>) was given at least 6 h after completion of O<sup>6</sup>-benzylguanine bolus. Treatment was repeated after recovery from toxicities at least 4 weeks apart for a maximum of 12 courses. Dose escalation followed the modified continual reassessment method. Pharmacokinetic analyses of temozolomide and 5-triazeno imidazole carboxamide (MTIC) were done in 28 patients. Results: A total of 44 and 26 eligible patients were enrolled on Str1 and Str2, respectively. Median age at study entry in each stratum was 8.6 and 11.3 years, respectively. Predominant diagnoses were high-grade/brainstem glioma in Str1 and medulloblastoma in Str2. Whereas the estimated MTDs of temozolomide for Str1 and Str2 were 562 and 407 mg/m<sup>2</sup>, respectively, the doses recommended for phase II investigations are 472 and 355 mg/m<sup>2</sup>, respectively. DLTs were predominantly neutropenia and thrombocytopenia. Three patients with gliomas experienced centrally confirmed partial responses to therapy. Four patients completed all planned therapy. Temozolomide and MTIC exposures were statistically associated with temozolomide dosage. Conclusions: The current schedule of temozolomide and O<sup>6</sup>-benzylguanine is safe and showed modest activity against recurrent brain tumors in children. 2007 American Association for Cancer Research.

Source: EMBASE

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91. A Phase II study of the farnesyl transferase inhibitor, tipifarnib, in children with recurrent or progressive high-grade glioma, medulloblastoma/ primitive neuroectodermal tumor, or brainstem glioma: A children's oncology group study
BACKGROUND. An open-label Phase II study of tipifarnib was conducted to evaluate its safety and efficacy in children with recurrent or refractory medulloblastoma (MB)/primitive neuroectodermal tumor (PNET), high-grade glioma (HGG), and diffuse intrinsic brainstem glioma (BSG).

METHODS. Between January 2004 and July 2005, patients were enrolled and stratified as follows: Stratum 1, recurrent or refractory MB/PNET; Stratum 2, recurrent or refractory HGG; and Stratum 3, recurrent or refractory BSG. Patients received tipifarnib 200 mg/m² per dose twice daily for 21 days repeated every 28 days. Patients who received enzyme-inducing anticonvulsants and other CYP3A4/5 inducers or inhibitors were excluded. The primary objective was to estimate the sustained response rate in all strata.

RESULTS. Ninety-seven patients with a median age of 11.2 years (range, 3.2-21.9 years) were enrolled on the study, and 81 patients were evaluable for response. One of 35 patients with BSG and 1 of 31 patients with HGG had a sustained partial response. No responses were observed in 15 patients with MB/PNET. Eight patients (3 HGG, 1 MB, and 4 BSG) remained stable for >=4 courses (range, 4-25 courses). The median number of courses received was 2 (range, 1-25 courses). The most frequent grade 3 and 4 toxicities included neutropenia (18.7%), thrombocytopenia (14.3%), and leukopenia (14.3%). The 6-month progression-free survival rate (+/-standard deviation) was 14% +/- 6% for HGG, 6% +/- 6% for MB/PNET and 3% +/- 3% for BSG.

CONCLUSIONS. Tipifarnib tolerated well but had little activity as a single agent in children with recurrent central nervous system malignancies.

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92. Treatment of newly diagnosed diffuse brain stem gliomas in children: In search of the holy grail

Author(s) Korones D.N.

Citation: Expert Review of Anticancer Therapy, May 2007, vol./is. 7/5(663-674), 1473-7140;1744-8328 (May 2007)

Publication Date: May 2007

Abstract: Diffuse brain stem glioma is the most devastating of pediatric malignancies. Virtually all children with this disease die within 1-2 years of diagnosis. After three decades of exhaustive research, the key to controlling this malignancy still eludes us. Attempts to improve survival using radiation, chemotherapy and biologic agents have yet to culminate in meaningful advances. Recent advances in molecular biology have led to the development of more targeted therapies, which are now being introduced in clinical trials for children with brain stem glioma. As our understanding of the biology of this disease improves, so too will our ability to target it more effectively. Real strides in improving the lives of children with brain stem glioma may finally be within our grasp.

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93. Phase I trial of imatinib in children with newly diagnosed brainstem and recurrent malignant gliomas: A Pediatric Brain Tumor Consortium report

This study estimated the maximum tolerated dose (MTD) of imatinib with irradiation in children with newly diagnosed brainstem gliomas, and those with recurrent malignant intracranial gliomas, stratified according to use of enzyme-inducing anticonvulsant drugs (EIACDs). In the brainstem glioma stratum, imatinib was initially administered twice daily during irradiation, but because of possible association with intratumoral hemorrhage (ITH) was subsequently started two weeks after irradiation. The protocol was also amended to exclude children with prior hemorrhage. Twenty-four evaluable patients received therapy before the amendment, and three of six with a brainstem tumor experienced dose-limiting toxicity (DLT): one had asymptomatic ITH, one had grade 4 neutropenia and, one had renal insufficiency. None of 18 patients with recurrent glioma experienced DLT. After protocol amendment, 3 of 16 patients with brainstem glioma and 2 of 11 patients with recurrent glioma who were not receiving EIACDs experienced ITH DLTs, with three patients being symptomatic. In addition to the six patients with hemorrhages during the DLT monitoring period, 10 experienced ITH (eight patients were symptomatic) thereafter. The recommended phase II dose for brainstem gliomas was 265 mg/m². Three of 27 patients with brainstem gliomas with imaging before and after irradiation, prior to receiving imatinib, had new hemorrhage, excluding their receiving imatinib. The MTD for recurrent high-grade gliomas without EIACDs was 465 mg/m², but the MTD was not established with EIACDs, with no DLTs at 800 mg/m². In summary, recommended phase II imatinib doses were determined for children with newly diagnosed brainstem glioma and recurrent high-grade glioma who were not receiving EIACDs. Imatinib may increase the risk of ITH, although the incidence of spontaneous hemorrhages in brainstem glioma is sufficiently high that this should be considered in studies of agents in which hemorrhage is a concern.

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94. Phase II study of thalidomide and radiation in children with newly diagnosed brain stem gliomas and glioblastoma multiforme

Author(s) Turner C.D., Chi S., Marcus K.J., MacDonald T., Packer R.J., Poussaint T.Y., Vajapeyam S., Ulrich N., Goumnerova L.C., Scott R.M., Briody C., Chordas C., Zimmerman M.A., Kieran M.W.

Citation: Journal of Neuro-Oncology, March 2007, vol./is. 82/1(95-101), 0167-594X;1573-7373 (March 2007)

Publication Date: March 2007

Abstract: A phase II study was conducted to assess the efficacy of administering daily thalidomide concomitantly with radiation and continuing for up to 1 year following radiation in children with brain stem gliomas (BSG) or glioblastoma multiforme (GBM). Secondary objectives were to obtain preliminary evidence of biologic activity of thalidomide and to evaluate toxicities from chronic administration of thalidomide in this population. Thirteen patients (2-14 years old) with newly diagnosed BSG (12 patients) or GBM (one patient) were enrolled between July 1999 and June 2000. All patients received focal radiotherapy to a total dose of 5,580 cGy. Thalidomide was administered once daily beginning on the first day of radiation and continued for 12 months or until the patient came off study. The starting dose was 12 mg/kg (rounded down to the nearest 50 mg) and was increased by 20% weekly, if tolerated, to 24 mg/kg or 1,000 mg (whichever was lower). Advanced imaging techniques and urine and serum analysis for anti-angiogenic markers were performed in some patients in an attempt to correlate changes with clinical effect of therapy. No patients completed the planned 12 months of thalidomide therapy and all have
since died of disease progression. The median duration of therapy was 5 months (range 2-11 months). Nine patients came off study for progressive disease (PD), three patients due to toxicity and one patient withdrew consent. Several patients on this study required more extended courses of high dose steroids than would have been otherwise expected for this population due to significant peritumoral edema and necrosis. No consistent pattern emerged from the biologic correlative studies from 11 patients. However, advanced imaging with techniques such as MR spectroscopy, MR perfusion and 18-fluorodeoxyglucose positron emission tomography (FDG-PET) were helpful in distinguishing growing tumor from treatment effect and necrosis in some patients. The median time to progression (TTP) was 5 months (range 2-11 months) and the median time to death (TTD) was 9 months (range 5-17 months). In this small patient sample adding thalidomide to radiation did not improve TTP or TTD from historical controls, however, toxicity appeared to be increased. Springer Science+Business Media, LLC 2006.

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95. Advances toward an understanding of brainstem gliomas

Author(s) Donaldson S.S., Laningham F., Fisher P.G.

Citation: Journal of clinical oncology : official journal of the American Society of Clinical Oncology, March 2006, vol./is. 24/8(1266-1272), 1527-7755 (10 Mar 2006)

Publication Date: March 2006

Abstract: The diagnosis of brainstem glioma was long considered a single entity. However, since the advent of magnetic resonance imaging in the late 1980s, neoplasms within this anatomic region are now recognized to include several tumors of varying behavior and natural history. More recent reports of brainstem tumors include diverse sites such as the cervicomedullary junction, pons, midbrain, or the tectum. Today, these tumors are broadly categorized as either diffuse intrinsic gliomas, most often in the pons, or the nondiffuse brainstem tumors originating at the tectum, focally in the midbrain, dorsal and exophytic to the brainstem, or within the cervicomedullary junction. Although we briefly discuss the nondiffuse tumors, we focus specifically on those diffuse brainstem tumors that regrettably still carry a bleak prognosis.

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96. Endoscopic third ventriculocisternostomy for brainstem tumors

Author(s) Klimo Jr. P., Goumnerova L.C.

Citation: Journal of Neurosurgery, October 2006, vol./is. 105 PEDIATRICS/SUPPL. 4(271-274), 0022-3085;0022-3085 (October 2006)

Publication Date: October 2006

Abstract: Object. The authors retrospectively reviewed the charts of all patients harboring brainstem tumors treated at their institution, excluding those with tectal gliomas, who underwent an endoscopic third ventriculocisternostomy. Methods. Endoscopic third ventriculocisternostomy was performed in 13 patients with tumors involving the brainstem: nine patients with diffuse pontine gliomas, two with posterior fossa ependymomas, one with a cervicomedullary tumor, and one with a pontine primitive neuroectodermal tumor. No technical difficulties attributable to the location of the tumors or surgery-related complications were encountered. Immediate symptomatic relief of hydrocephalus was achieved in all patients, and there was an associated decrease in steroid and analgesic agent requirements. Only one patient eventually required a shunt. Conclusions. Endoscopic third ventriculocisternostomy can be used in the terminal treatment of patients with brainstem tumors, yielding good results without significant surgical morbidity.

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97. Maintenance treatment with interferon-gamma and low-dose cyclophosphamide for pediatric high-grade glioma


Citation: Journal of Neuro-Oncology, September 2006, vol./is. 79/3(315-321), 0167-594X;1573-7373 (September 2006)

Publication Date: September 2006

Abstract: Background: The prognosis of high-grade glioma in children is poor. Purpose: Interferon-gamma may increase the immune surveillance of glioma cells. Earlier clinical evidence had shown that low dose cyclophosphamide (CPM) increased immune response. Methods: After induction treatment with simultaneous radiation and chemotherapy, patients were treated with individually increasing interferon-gamma (IFN-γ) doses starting from 25 μg/m²/d s.c. increasing up to a maximum of 175 μg/m²/d within 7 weeks. Cyclophosphamide was given at 300 mg/m² i.v. every 21 days. Forty pediatric glioma patients were enrolled (median age: 8.5 year, male: n = 22). Tumor locations included cerebral cortex (n = 8), basal ganglia (n = 4), brainstem (n = 24), cerebellum (n = 3), spinal cord (n = 1). Histologies were GBM (n = 14), AA (n = 14), LGG (n = 2, diffuse intrinsic pontine glioma). There was grade IV toxicity for thrombocytopenia (10%) and leucopenia (2.5%), grade III toxicity for central nervous (2.5%) and hepatic (5%) side effects, no toxic death. The observation time of the six surviving patients was: 1.2, 1.9, 4.2, 4.4, 4.6 and 4.7 years respectively. The median overall survival (1 year) was not significantly different from a historical control group (0.8 years). The survival of pontine gliomas appeared even inferior when compared to the previous protocol (n.s.). Conclusion: Maintenance treatment with IFN-γ and low dose CPM has no sufficient beneficial effect for the treatment of high-grade glioma. Springer Science+Business Media B.V. 2006.

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98. Treatment options in childhood pontine gliomas


Citation: Journal of Neuro-Oncology, September 2006, vol./is. 79/3(281-287), 0167-594X;1573-7373 (September 2006)

Publication Date: September 2006

Abstract: Background: Pontine gliomas are the subgroup of brainstem gliomas with the worst prognosis. Controversial treatment approaches are discussed. Patients and methods: Data of children with pontine gliomas treated in different prospective multi-center studies who were registered in the HIT-GBM database were pooled and analyzed addressing prognostic factors and the relevance of intensive treatment using contingency tables, Kaplan-Meier curves and Cox regression analyses. Results: From 1983 to 2001, 153 patients (74 males, 79 females, mean age: 8.1 years) with pontine gliomas were registered. Twenty-one tumors were low-grade and 60 were high-grade gliomas (72 undefined histology: 67 no surgery, 5 incomplete data). Sixteen tumors were partially resected, and 125 were irradiated. Ninety children received chemotherapy according to the "HIT-GBM" protocols ("Hirntumor-Glioblastoma multiforme"). The one-year overall survival rate (1YOS) of all patients with pontine glioma was 39.9 +/- 4.3%. None of the surviving patients had an observation time longer than 3.9 years. Favorable prognostic factors seemed to be age younger than 4 years, low-grade histology and smaller tumor. All three major treatment modalities including resection, irradiation and chemotherapy had prognostic relevance in univariable analysis. Chemotherapy remained beneficial, even if the analysis was restricted to the subgroup of irradiated tumors (1YOS 45.8 +/- 5.4% vs. 34.4 +/- 13.5%, P = 0.030). Conclusion: Irradiation is an effective element for the treatment of pontine gliomas.
Intensive chemotherapy seems to be important in achieving a better OS. Springer Science+Business Media, Inc. 2006.

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**Citation:** Journal of Neuro-Oncology, June 2006, vol./is. 78/2(199-205), 0167-594X;1573-7373 (June 2006)

**Publication Date:** June 2006

**Abstract:** The aim of the present study was to evaluate the spectrum of late effects in a large cohort of pediatric patients with low-grade gliomas (WHO grade I and II) during an observation period of 20 years. Eighty-seven patients with low-grade gliomas grouped according to tumor location (cerebellum: n = 28; cerebral hemispheres: n = 21; central midline: n = 15; brainstem: n = 12; tectum: n = 5; other locations: n = 6) were evaluated for tumor- and/or treatment-related late effects by analysis of medical and computer records, and personal interviews. Seventy patients underwent neurosurgery, 29 patients received additional radiotherapy and 20 additional chemotherapy. Median follow-up of survivors is 96 months with an overall survival of 79% (cerebellum: 89%; cerebral hemispheres: 95%; central midline: 80%; brainstem: 25%; tectum: 100%; other locations: 66%). Chronic medical problems (mild ataxia to multiple severe neuroendocrine deficits) are observed in 100% of patients with brainstem/central midline tumors and in 40-50% of patients with low-grade gliomas of other locations. Endocrine deficiencies were observed in 15/17 (88%) of long-term survivors who received radiotherapy. In contrast, none of the patients who underwent surgery only had endocrine deficiencies. Seven long-term survivors (10.1%) are severely disabled with permanent need of medical help. Tumor- and treatment-related late effects are common in patients with low-grade gliomas with the most severe occurring in patients with brainstem or central midline tumors. As long-term survival is excellent in patients with low-grade gliomas except for tumors located in the brainstem, future treatment studies should focus on avoiding long-term late effects. Springer Science+Business Media, Inc. 2006.

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100. Phase II trial of intravenous lobradimil and carboplatin in childhood brain tumors: A report from the Children’s Oncology Group


**Citation:** Cancer Chemotherapy and Pharmacology, September 2006, vol./is. 58/3(343-347), 0344-5704 (September 2006)

**Publication Date:** September 2006

**Abstract:** Background: Lobradimil is a synthetic bradykinin analog that rapidly and transiently increases the permeability of the blood-brain barrier (BBB). The combination of lobradimil and carboplatin was studied in pediatric patients with primary brain tumors in a phase II trial, the primary endpoints of which were to estimate the response rate and time to disease progression. Patients and methods: Patients were stratified by histology into five cohorts: brainstem glioma, high-grade glioma, low-grade glioma, medulloblastoma/primitive neuroectodermal tumor (PNET), and ependymoma. Patients received carboplatin adaptively dosed to achieve a target AUC of 3.5 mg min/ml per day (7 mgmin/ml/cycle) intravenously over 15 min on 2 consecutive days and lobradimil 600 ng/kg ideal body
weight/day on 2 consecutive days each 28 day cycle. Results: Forty-one patients, age 2-19 years, were enrolled; 38 patients, including 1 patient ultimately determined to have atypical neurocytoma, were evaluable for response. No objective responses were observed in the brainstem glioma (n=12) and high-grade glioma (n=9) cohorts, although two patients with high-grade glioma had prolonged disease stabilization (>6 months). The study was closed for commercial reasons prior to achieving the accrual goals for the ependymoma (n=8), medulloblastoma/PNET (n=6) and low-grade glioma (n=2) cohorts, although responses were observed in 1 patient with PNET and 2 patients with ependymoma. Conclusion: The combination of lobradimil and carboplatin was inactive in childhood high-grade gliomas and brainstem gliomas. Springer-Verlag 2006.

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101. Temozolomide in resistant or relapsed pediatric solid tumors

Author(s) De Sio L., Milano G.M., Castellano A., Jenkner A., Fidani P., Dominici C., Donfrancesco A.

Citation: Pediatric Blood and Cancer, July 2006, vol./is. 47/1(30-36), 1545-5009;1545-5017 (July 2006)

Publication Date: July 2006

Abstract: Purpose. We report the off-label study aimed at investigating the use of temozolomide (TMZ) as single agent in relapsed or resistant pediatric solid tumors. The drug was administered at the dose of 215 mg/m^2/day x 5 days or 180 mg/m^2/day x 5 days in patients with prior craniospinal irradiation (CSI) or autologous bone marrow transplantation (ABMT). Patients and Methods. Fifty two patients, median age 127.6 months, with resistant or relapsed solid tumors were enrolled. Tumor types were: neuroblastoma (NB; n = 17), medulloblastoma (MB; 8), brain stem glioma (BSG; 8), extraosseous Ewing's sarcoma/peripheral neuroectodermal tumor (EOES; 4), Ewing's sarcoma (ES; 4), anaplastic astrocytoma (AA; 3), rhabdomyosarcoma (RMS; 2), ependymoma (EP; 2), cerebral primitive neuroectodermal tumor (cPNET; 2), hepatocarcinoma (HC; 1), and osteosarcoma (OS; 1). All patients were pre-treated. Two outpatient courses were administered, with a median of 4.8 courses/pt. Results. Objective response-rate (CR + PR + MR) in our series was 13.4% (1.9% CR, 3.8% PR, and 7.7% MR), SD occurred in 38.4% of patients and 48% had PD. The median survival was 7.8 months (range 1-37) and median time to progression was 3.4 months (range 1-20); these data were significantly correlated with histology and previous nitrosureas administration in multivariate analysis. Haematological toxicity grade 3-4 (mainly thrombocytopenia) was observed in 21.4% of administered courses, nausea was reported in 3.1% and respiratory distress in 0.7%. Conclusion. Oral TMZ was well tolerated in children with resistant or relapsed solid tumors and showed activity in NB and CNS tumours refractory to standard chemotherapy. 2005 Wiley-Liss, Inc.

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102. Brainstem gliomas

Author(s) Jallo G.

Citation: Child's Nervous System, January 2006, vol./is. 22/1(1-2), 0256-7040 (January 2006)

Publication Date: January 2006

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103. Far lateral suprarebellar infratentorial approach for the treatment of upper brainstem gliomas: Clinical experience with pediatric patients

Author(s) Vougioukas V.I., Omran H., Glasker S., Van Velthoven V.

Citation: Child's Nervous System, December 2005, vol./is. 21/12(1037-1041), 0256-7040 (December 2005)

Publication Date: December 2005

Abstract: Objective: Surgical exposure of intrinsic lesions located lateral to the brainstem still represents a challenging task. The aim of this study was to assess the feasibility of the extracerebral far lateral suprarebellar infratentorial (FLSI) approach for the treatment of gliomas located in the upper brainstem in the pediatric population. Methods and results: Between 1992 and 2002, seven patients (mean age 8.7 years) with tumors of glial origin (WHO I-IV) located mainly in the pontomesencephalic region were operated with the FLSI approach in a sitting position. Satisfactory extent of resection without additional morbidity was achieved. Conclusion: In a carefully selected pediatric patient population, the FLSI approach proved to be a feasible and effective surgical route for the treatment of upper brainstem gliomas. Springer-Verlag 2005.

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104. The treatment of high grade gliomas and diffuse intrinsic pontine tumors of childhood and adolescence: A historical - and futuristic - perspective

Author(s) Finlay J.L., Zacharoulis S.

Citation: Journal of Neuro-Oncology, December 2005, vol./is. 75/3(253-266), 0167-594X;1573-7373 (December 2005)

Publication Date: December 2005

Abstract: Pediatric high grade gliomas represent a heterogeneous group of tumors with poor prognoses despite the use of multimodal treatment. Very little progress has been made over the past decades in identifying efficacious therapeutic modalities against both high grade gliomas and diffuse brainstem gliomas in children. The degree of surgical resection is the most important clinical prognostic factor for children with high grade gliomas, and a complete resection should be attempted whenever feasible. The role of radiation therapy in the treatment of older children with high grade gliomas and diffuse brain stem gliomas is undisputed; however the benefit of using radiation for patients less than 6 years of age (with high grade gliomas) might be questionable. Despite the absence of solid evidence to support its use, chemotherapy is routinely used against these tumors. Currently temozolomide is being investigated due to its activity in adult trials and based on preliminary data regarding recurrent disease. A small subgroup of patients can be successfully treated with high dose chemotherapy followed by autologous stem cell rescue. Early trials using this modality in the past had been associated with high morbidity and mortality. High dose chemotherapy with autologous stem cell rescue in selected patients with minimal residual disease, angiogenesis inhibitors, radiosensitizers and other biological modifiers are being currently investigated in phase I/II trials. Springer 2005.

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105. Topotecan as a radiosensitizer in the treatment of children with malignant diffuse brainstem gliomas: Results of a French Society of Paediatric Oncology Phase II Study

Author(s) Bernier-Chastagner V., Grill J., Doz F., Bracard S., Gentet J.C., Marie-Cardine
BACKGROUND. The current Phase II study was conducted to evaluate the survival and toxicity observed in children with newly diagnosed brainstem gliomas who were treated with the daily radiotherapy with topotecan used as a radiosensitizer.

METHODS. Eligible patients were those ages 3-18 years with previously untreated tumors arising in the pons diagnosed within the previous 6 months. Histologic confirmation was not mandatory provided that the clinical and magnetic resonance imaging findings were typical for a diffusely infiltrating brainstem lesion. Treatment was comprised of a 6-week course of topotecan administered intravenously at a dose of 0.4 mg/m$^2$/day over 30 minutes within 1 hour before irradiation. Radiotherapy was comprised of a once-daily treatment of 1.8 grays (Gy) per fraction to a total dose of 54 Gy. RESULTS. Thirty-two patients were included in the current study between August 2000 and October 2002. All patients completed the combined treatment in accordance with the treatment design. Only partial responses were observed, occurring in 40% of the patients. The 9-month and 12-month survival rates were 34.4% +/- 8% and 25.5% +/- 8%, respectively. The median duration of survival for these 32 patients was 8.3 months. An intratumoral cystic/necrotic change was observed in five patients, with clinical impairment noted in two patients. One intratumoral hemorrhage occurred during radiotherapy, and was associated with transitory neurologic impairment. CONCLUSIONS. The findings of the current study regarding newly diagnosed brainstem glioma patients treated with topotecan given as a radiosensitizing agent did not reproduce the encouraging results obtained in preclinical studies. Therefore, the concomitant combination of topotecan and radiotherapy at this schedule and these doses cannot be recommended for the treatment of patients with brainstem gliomas. 2005 American Cancer Society.

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106. A phase I study of concurrent RMP-7 and carboplatin with radiation therapy for children with newly diagnosed brainstem gliomas


Citation: Cancer, October 2005, vol.is. 104/9(1968-1974), 0008-543X (26 Oct 2005)

Abstract: BACKGROUND. Ninety percent of children with diffuse, intrinsic brainstem tumors will die within 18 months of diagnosis. Radiotherapy is of transient benefit to these children, and a potential way to improve its efficacy is to add radiosensitizers. Carboplatin is antineoplastic and radiosensitizing; however, its delivery to the primary tumor site is problematic. RMP-7 is a bradykinin analog that causes selective permeability of the blood-brain-tumor interface. The objective of this Phase 1 study was to determine the toxicity and feasibility of delivering RMP-7 and carboplatin for 5 successive days during radiotherapy to children with newly diagnosed, diffuse, intrinsic brainstem gliomas. METHODS. RMP-7 was given prior to the end of carboplatin infusion. Local radiotherapy, in dose fractions of 180 centigrays (cGy) per day (to a total dose of 5940 cGy), was given within 4 hours of completion of drug delivery. Duration of treatment was escalated in a stepwise, weekly fashion in cohorts of 3 patients, until there was treatment-limiting toxicity or until radiotherapy was completed. Thirteen patients were treated, and their median age was 7 years (age range, 3-12 yrs). RESULTS. One child died early during treatment of progressive disease and was not assessable for toxicity. Treatment for 3 weeks, 4 weeks, and 5 weeks was tolerated well, with mild flushing, tachycardia, nausea, emesis, dizziness, and abdominal pain. One of 3 children treated at the full duration of therapy (33 doses over 7 weeks) developed dose-limiting hepatotoxicity and neutropenia. The estimated median survival was 328 days, and 1 patient remained free of disease progression for > 400 days.
after the initiation of treatment. CONCLUSIONS. The results of this study confirmed the feasibility of giving RMP-7 and carboplatin daily during radiotherapy to children with brainstem tumors. 2005 American Cancer Society.

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107. Etoposide, vincristine, and cyclosporin a with standard-dose radiation therapy in newly diagnosed diffuse intrinsic brainstem gliomas: A pediatric oncology group phase I study

Author(s) Greenberg M.L., Fisher P.G., Freeman C., Korones D.N., Bernstein M., Friedman H., Blaney S., Hershon L., Zhou T., Chen Z., Kretschmar C.

Citation: Pediatric Blood and Cancer, October 2005, vol./is. 45/5(644-648), 1545-5009 (15 Oct 2005)

Publication Date: October 2005

Abstract: Background. Brainstem gliomas (BSGs) are resistant to all therapy. Based on their imaging characteristics, we postulated that inhibition of P-glycoprotein (P-gp) associated with endothelial cells of the blood-brain barrier might enhance penetration of xenobiotic antineoplastics. Procedure. Seven patients were enrolled in a Phase I study of etoposide, continuous infusion cyclosporine A given with and escalating doses of vincristine and concomitant standard-dose irradiation. Results. Six patients were entered at the first level and one at the second. Closure of the study was mandated by dose-limiting neurotoxicity, consisting of seizures associated with white-matter changes, and alteration of consciousness with bulbar signs. One patient had tumor necrosis at 6 weeks, suggesting some tumor effect. Median survival for the group was 11 months, and for the patients who completed more than 1 month of therapy it was 11 months. Conclusion. This regimen proved excessively toxic. 2005 Wiley-Liss, Inc.

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108. Phase 1 study of concurrent RMP-7 and carboplatin with radiotherapy for children with newly diagnosed brainstem gliomas


Citation: Cancer, September 2005, vol./is. 104/6(1281-1287), 0008-543X (15 Sep 2005)

Publication Date: September 2005

Abstract: BACKGROUND. Ninety percent of children with diffuse intrinsic brainstem tumors will die within 18 months of diagnosis. Radiotherapy is of transient benefit, and one way to potentially improve its efficacy is to add radiosensitizers. Carboplatin is antineoplastic and radiosensitizing. However, delivery to the primary tumor site is problematic. RMP-7 is a bradykinin analog that causes selective permeability of the blood-brain-tumor interface. The goal of the current Phase I study was to determine the toxicity and feasibility of delivering RMP-7 and carboplatin for 5 successive days during radiotherapy. METHODS. RMP-7 was given before the end of carboplatin infusion. Local radiotherapy (5940 centigrays) was given within 4 hours of completion of drug delivery. Duration of treatment wasescalated in a stepwise, weekly fashion, in cohorts of 3, until there was treatment-limiting toxicity or until radiotherapy was completed. Thirteen patients were treated, whose median age was 7 years (range, 3-14 yrs). RESULTS. One child died early in treatment of progressive disease and was not assessable for toxicity. Treatment for 3, 4, or 5 weeks was tolerated well, with mild flushing, tachycardia, nausea, emesis, dizziness, and abdominal pain. Of 3 children treated at the full duration of therapy (33 doses over 7 wks), 1 developed dose-limiting hepatotoxicity and neutropenia. The
estimated median survival period was 328 days, and 1 patient remained disease progression free > 400 days from initiation of treatment. CONCLUSIONS. The results of the current study confirmed the feasibility of giving RMP-7 and carboplatin daily during radiotherapy. 2005 American Cancer Society.

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109. Role of temozolomide after radiotherapy for newly diagnosed diffuse brainstem glioma in children: Results of a multiinstitutional study (SJHG-98)

Author(s) Broniscer A., Iacono L., Chintagumpala M., Fouladi M., Wallace D., Bowers D.C., Stewart C., Krasin M.J., Gajjar A.

Citation: Cancer, January 2005, vol./is. 103/1(133-139), 0008-543X (01 Jan 2005)
Publication Date: January 2005

Abstract: BACKGROUND. The role of chemotherapy in the treatment of children with newly diagnosed diffuse brainstem glioma is uncertain. In the current study, the authors tested the efficacy of temozolomide treatment after radiotherapy (RT) in this setting.

METHODS. Patients ages 3-21 years were eligible for the current multiinstitutional study. An optional window therapy regimen consisting of 2 cycles of intravenous irinotecan (10 doses of 20 mg/m² per day separated by 2 days of rest per cycle) was delivered over 6 weeks and was followed by conventionally fractionated HT. The 5-day schedule of temozolomide (200 mg/m² per day) was initiated 4 weeks after RT and was continued for a total of 6 cycles. The pharmacokinetics of temozolomide and its active metabolite, 5-(3-methyltriazen-1-yl)imidazole-4-carboxamide (MTIC), were analyzed during Cycles 1 and 3. RESULTS. Thirty-three patients (median age at diagnosis, 6.4 years) were enrolled. Of the 16 patients who received window therapy, 6 had irinotecan treatment discontinued due to clinical progression (n = 5) or toxicity (n = 1); the remaining 10 experienced disease stabilization after 2 cycles. All patients completed RT (median dose, 55.8 gray). Twenty-nine patients received a combined total of 125 cycles of temozolomide. Grade 3/4 neutropenia and thrombocytopenia occurred in 33% and 29% of all temozolomide cycles, respectively. In approximately one-third of the cycles, dose reduction was required due to myelosuppression. No correlation was demonstrated between temozolomide/MTIC exposure and myelosuppression at the conclusion of Cycle 1. All patients died of disease progression (median survival, 12 months). The estimated 1-year survival rate was 48% (standard error, 8%). CONCLUSIONS. The administration of temozolomide after RT did not alter the poor prognosis associated with newly diagnosed diffuse brainstem glioma in children. 2004 American Cancer Society.

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110. Radiotherapy for high-grade gliomas: Does altered fractionation improve the outcome?

Author(s) Nieder C., Andratschke N., Wiedenmann N., Busch R., Grosu A.L., Molls M.

Citation: Strahlentherapie und Onkologie, July 2004, vol./is. 180/7(401-407), 0179-7158 (July 2004)
Publication Date: July 2004

Abstract: Background and Purpose: The publication of Radiation Therapy Oncology Group (RTOG) Study 83-02 in 1996 stimulated further investigations of altered fractionation, i.e., application of more than one fraction per day, in high-grade gliomas. This review summarizes the results of trials published between January 1997 and June 2002. Material and Methods: To identify suitable trials, a Medline search was performed by use of the
following key words: brain tumors/astrocytoma/glioma/high-grade glioma/malignant glioma/glioblastoma multiforme and accelerated radiotherapy/hyperfractionated radiotherapy/altered fractionation. In addition, the search was extended to reference lists of articles and textbooks. Whenever possible, data were extracted from the original papers on an intention-to-treat basis, i.e., patients with protocol violations were not excluded for the purpose of this analysis. Studies in brain stem gliomas, pediatric patients and studies which achieved acceleration by radiosurgery, stereotactic radiotherapy, or brachytherapy rather than conventional external-beam treatment were not included. An exploratory analysis of 2-year survival was also performed. For this purpose, the 2-year survival rate was extracted from each individual study. The total number of 2-year survivors was then calculated for each treatment strategy and compared by use of the chi<sup>2</sup>-test. Results: The authors identified 1,414 patients from 21 studies; two of these were randomized phase III studies. In seven studies (658 patients), chemotherapy or radiosensitizers were not administered in addition to radiotherapy. The others provide a very heterogeneous set of data, because a large variety of drugs and administration schedules was used. Seven studies included patients with glioblastoma multiforme only, two were limited to patients with anaplastic gliomas. Dose per fraction was 1.2-1.8 Gy in 17 studies and 1.9-2.65 Gy in four. Overall treatment time was 12-31 days, except for one study. Three out of five studies where three fractions per day were administered, included a 2-week break (split-course studies). None of the studies reported a significant improvement in survival by altered fractionation in comparison to either institutional historical controls or their respective randomized control arm. Doses of 60-70 Gy do not appear to improve survival compared to 50-60 Gy. The current data provide no arguments for use of three instead of two fractions per day. Median survival was 10 months after radiotherapy alone (658 patients) and 11 months after combined treatment (756 patients). Regarding 2-year survival rates, radiotherapy alone resulted in 13%, combined chemoradiation or use of sensitizers in 23% (p < 0.0001). However, prognostic factors such as tumor histology were not equally distributed and favor the combined-treatment group. Evaluation of six studies of conventional radiotherapy alone resulted in data from 571 patients. Their median survival was 10.8 months. Cumulative 2-year survival amounted to 15%. The studies of conventional radiotherapy plus chemotherapy or sensitizers included 1,115 patients with a median survival of 11 months (2-year survival rate 18.5%). Conclusion: Altered fractionation shortens the overall treatment time for adult patients with supratentorial high-grade gliomas. However, there is no significant survival improvement.

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111. Oral Topotecan in Children with Recurrent or Progressive High-Grade Glioma: A Phase I/II Study by the German Society for Pediatric Oncology and Hematology


Citation: Cancer, April 2004, vol./is. 100/8(1750-1757), 0008-543X (15 Apr 2004)

Publication Date: April 2004

Abstract: BACKGROUND. Continuous oral treatment with topotecan may be more effective than the typical 1-day and 5-day treatment schedules. In previous studies of continuous treatment with topotecan, increased intestinal side effects were reported in adult patients; however, the experience in pediatric patients and patients with high-grade glioma is quite limited. METHODS: Thirty-two pediatric patients with recurrent high-grade glioma (16 females and 16 males; median age, 9.5 years) were enrolled in the current Phase I/II study. Tumor locations included the cerebral cortex (n = 5), pons (n = 18), and other sites (n = 9). An injectable formulation of topotecan was administered orally, in ice-cold orange juice, once daily. The starting dose of 0.4 mg/m<sup>2</sup> per day was escalated on a patient-by-patient basis. At each patient's maximum dose, blood samples were obtained for the determination of plasma hydroxytopotecan and topotecan lactone concentrations and for the calculation of pharmacokinetic quantities. RESULTS. The toxicity criteria for a maximum tolerated topotecan dose were met in only 19 patients. The primary toxicity type was hematologic. The median maximum tolerated dose was 0.9 mg/m<sup>2</sup> per day (n = 19). The calculated maximum total plasma topotecan concentration was 3.8 ng/mL.
(n = 7), with an area under the concentration-time curve of 38.4 ng hours/mL and a half-life of 4.1 hours, which would result in the complete disappearance of topotecan from the plasma after 12 hours. Objective responses were observed in 2 of 13 evaluable patients and lasted for 2.5 and 9 months, respectively (continuous clinical remission, 1 of 14 patients; partial response, 2 of 14 patients; stable disease, 7 of 14 patients; progressive disease, 4 of 14 patients). CONCLUSIONS. Oral topotecan (median dose, 0.9 mg/m² per day) administered once daily was well tolerated and somewhat effective in children with recurrent high-grade glioma. A schedule in which the daily dose is split so that dosing is performed twice daily may be superior to the current schedule. 2004 American Cancer Society.

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112. A phase I study of topotecan as a radiosensitizer for brainstem glioma of childhood: first report of the Children's Cancer Group-0952

Author(s) Sanghavi S.N., Needle M.N., Krailo M.D., Geyer J.R., Ater J., Mehta M.P.

Citation: Neuro-oncology, January 2003, vol./is. 5/1(8-13), 1522-8517 (Jan 2003)

Publication Date: January 2003

Abstract: Our purpose was to establish the maximum tolerated dosage (MTD) of daily i.v. topotecan with conventionally fractionated radiotherapy (XRT) for patients with intrinsic pontine glioma of childhood. Topotecan was given as a 30-min i.v. infusion 30-60 min before each XRT treatment given daily for 33 days. Total XRT dose was 59.4 Gy. Dose escalation of topotecan was carried out using a standard phase I design. Dose limiting toxicity (DLT) was defined as an absolute neutrophil count (ANC) of \(< or =500/mm(3)\) for > or =7 days; platelets of \(< or =50,000/mm(3)\) for > or =7 days; >7 days platelet transfusions; fever and neutropenia (ANC \(< or =500/mm(3)\) for > or =7 days); and/or any > or=grade 3 non-hematologic toxicity. In this multi-institutional phase I study, 17 patients <21 years with intrinsic pontine glioma were enrolled. Sixteen patients completed treatment. An ANC \(< or =500/mm(3)\) for > or =7 days occurred in 2/5 patients at 0.50 mg/m(2) of topotecan, which was the DLT. The remaining 14 patients received topotecan without experiencing DLT. One patient at 0.40 mg/m(2) died of disease progression while on treatment. There were 6 other grade 4 hematologic events (5 ANCs <500/mm(3), 1 hemoglobin <6.5 g/dl) not meeting DLT criteria. No significant non-hematologic toxicities were seen. The actuarial median survival time is 15 months (95% confidence interval, 9.6-19 months); 1-year survival is 53%. DLT of daily topotecan with cranial XRT is grade 4 neutropenia for > or =7 days at 0.50 mg/m(2) x 33 (total dosage = 16.5 mg/m(2)); the recommended safe MTD of daily topotecan for further phase II testing is 0.40 mg/m(2) x 33 (total dosage = 13.2 mg/m(2)).

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113. Preradiation chemotherapy in primary high-risk brainstem tumors: Phase II study CCG-9941 of the Children's Cancer Group


Citation: Journal of Clinical Oncology, August 2002, vol./is. 20/16(3431-3437), 0732-183X (15 Aug 2002)

Publication Date: August 2002

Abstract: Purpose: This Children's Cancer Group group-wide phase II trial evaluated the
efficacy and toxicity of two chemotherapy arms administered before hyperfractionated external-beam radiotherapy (HFEBRT). Patients and Methods: Thirty-two patients with newly diagnosed brainstem gliomas were randomly assigned to regimen A and 31 to regimen B. Regimen A comprised three courses of carboplatin, etoposide, and vincristine; regimen B comprised cisplatin, etoposide, cyclophosphamide, and vincristine. Both arms included granulocyte colony-stimulating factor. Patients were evaluated by magnetic resonance imaging after induction chemotherapy and HFEBRT at a dose of 72 Gy. Results: Ten percent +/- 5% of regimen A patients objectively responded to chemotherapy. For combined induction and radiotherapy, 27% +/- 9% of patients improved. The neuroradiographic response rate for regimen B was 19% +/- 8% for chemotherapy and 23% +/- 9% after HFEBRT. Response rates were not statistically significant between regimens after induction or chemotherapy/HFEBRT. Event-free survival was 17% +/- 5% (estimate +/- SE) at 1 year and 6% +/- 3% at 2 years. Survival was significantly longer among patients who responded to chemotherapy (P < .05). Among patients who received regimen A induction, grades 3 and 4 leukopenia were observed in 50% to 65%, with one toxicity-related death. For regimen B, severe leukopenia occurred in 86% to 100%, with febrile neutropenia in 48% to 60% per course. Conclusion: Neither chemotherapy regimen meaningfully improved response rate, event-free survival, or overall survival relative to previous series of patients with brainstem gliomas who received radiotherapy with or without chemotherapy. 2002 by American Society of Clinical Oncology.

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114. Brain stem gliomas
Author(s) Guillamo J.-S., Doz F., Delattre J.-Y.
Citation: Current Opinion in Neurology, 2001, vol./is. 14/6(711-715), 1350-7540 (2001)
Publication Date: 2001
Abstract: Brainstem gliomas are now regarded as a heterogeneous group of tumors that can be distinguished by age of onset, clinical and radiological presentation and biological behavior. This paper will focus on each subtype of tumor, in children and in adults, and on recent advances in diagnostic criteria and therapeutic options. 2001 Lippincott Williams & Wilkins.
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115. Outcome and long-term side effects after synchronous radiochemotherapy for childhood brain stem gliomas
Citation: Pediatric Neurosurgery, 2001, vol./is. 35/4(173-180), 1016-2291 (2001)
Publication Date: 2001
Abstract: Between 1993 and 1999, 11 children with histologically confirmed diffuse and exophytic brain stem glioma (BSG) were treated with intensive induction chemotherapy and simultaneous external beam irradiation. Chemotherapy was performed according to the German/Austrian Pediatric Brain Tumor Study HIT ‘91 and included two cycles of ifosfamide (days 1-3), etoposide (days 4-6), methotrexate (days 15 and 22), cisplatin (days 29-31) and cytarabine (days 29-31), separated by a 3-week interval. Maintenance chemotherapy with carmustine, carboplatin and vincristine (8 cycles over a 1-year period) was given in those patients who responded clinically or radiographically to induction chemotherapy. Six of 11 patients showed an objective reduction in tumor size on magnetic resonance imaging and 4 of 11 are alive in good general condition >22, >22, >90 and >92.
months, respectively, after diagnosis without radiographic evidence of tumor progression (1 complete remission, 2 partial remissions, 1 stable disease), but suffer from moderate to severe long-term side effects. Three patients died due to disease progression after having achieved a partial remission which lasted 5, 6 and 18 months, respectively, whereas only short-term stabilization was observed in 4 patients who died within 1 year after diagnosis. Acute hematologic toxicity was severe but manageable. This intensive combined modality treatment was toxic but yielded objective responses in more than 50% and long-term survivors in one third of childhood BSG patients. Copyright 2001 S. Karger AG, Basel.

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Citation: Journal of Pediatric Hematology/Oncology, 2000, vol./is. 22/1(41-44), 1077-4114 (2000)

Publication Date: 2000

Abstract: Purpose: Children with recurrent or progressive central nervous system (CNS) tumors have an unfavorable prognosis. Based on Pediatric Oncology Group (POG) institutional pilot data, low-dose oral methotrexate (MTX) was studied. Methods: Eight dosages of MTX 7.5 mg/m^2 every 6 hours were administered on a weekly schedule for as long as 18 months. Patients in six different brain tumor strata were accrued. Results: The response rates (complete or partial responses) were as follows: astrocytoma 2 of 10, malignant glioma 1 of 19, medulloblastoma 0 of 18, brainstem tumor 0 of 12, ependymoma 1 of 7, and miscellaneous histologic types 0 of 12. The main toxicities, mucositis, myelosuppression, and hepatic transaminase elevation were considered tolerable. Conclusion: Low-dose oral MTX showed no significant activity against malignant glioma, medulloblastoma, brainstem tumors, and miscellaneous histologic types. Indeterminate but low response rates were observed in children with astrocytoma and ependymoma. This regimen will not be recommended for front-line therapy.

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117. Fractionated stereotactic conformal radiation therapy of brain stem gliomas: Outcome and prognostic factors

Author(s) Schulz-Ertner D., Debus J., Lohr F., Frank C., Hoss A., Wannenmacher M.

Citation: Radiotherapy and Oncology, November 2000, vol./is. 57/2(215-223), 0167-8140 (01 Nov 2000)

Publication Date: November 2000

Abstract: Background and purpose: Evaluation of outcome and prognostic factors in patients with brain stem glioma (BSG) following fractionated stereotactic radiotherapy (FSRT). Materials and methods: Between 1990 and 1997, we treated 41 patients with FSRT in a phase I/II trial. Median age was 24 years. Out of 36 patients with histologically proven glioma, ten had a partial tumour resection. Histology revealed low grade gliomas in 30 patients and anaplastic gliomas in six patients. A mean total dose of 54 Gy was given in daily fractions of 1.8 Gy. Median follow-up was 12 months. Results: Three patients died during FSRT. Neurological improvement was achieved in 19/38 patients. Reduction of tumour size was reported in 12/38, in 16 patients the lesion was unchanged, ten showed progression. Median time to progression was 23 months, median overall survival 40
months with an actuarial survival of 83% at 1 year, 55% at 3 years and 33% at 5 years. In 20 of 22 patients with recurrence progression was inside the target volume. Significant prognostic factors for survival were clinical and radiological response 6 weeks after FSRT. Treatment toxicity was mild. Ototoxicity occurred in one patient. Conclusions: FSRT is a feasible treatment modality for BSG with tolerable toxicity. The risk of marginal failure is low. Copyright (C) 2000 Elsevier Science Ireland Ltd.

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118. Surgical management of intrinsic brain stem gliomas

Author(s) Bricolo A.
Citation: Operative Techniques in Neurosurgery, 2000, vol./is. 3/2(137-154), 1092-440X (2000)
Publication Date: 2000
Abstract: During the last 2 decades, the management of brain stem gliomas has evolved toward a more aggressive surgical treatment. Accrued experience with intra-axial lesions has shown that direct resection can be performed with minimal morbidity in subgroups of lesions previously managed conservatively by radiotherapy. This article reviews the criteria for selecting tumors amenable for surgery and associated technical strategies for removal. Copyright (C) 2000 by W.B. Saunders Company.
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119. Surgical management of cervicomedullary and dorsally exophytic brain stem tumors

Author(s) Jallo G.I., Kothbauer K.F., Epstein F.J.
Citation: Operative Techniques in Neurosurgery, 2000, vol./is. 3/2(131-136), 1092-440X (2000)
Publication Date: 2000
Abstract: Cervicomedullary and dorsally exophytic brain stem tumors are surgically accessible and treatable neoplasms that must be distinguished as a specific subset of brain stem gliomas. Brain stem gliomas account for only 10% to 20% of all pediatric brain tumors, and the diffuse neoplasm has been thought of historically when describing these tumors. The focal dorsally exophytic brain stem and cervicomedullary glioma constitute about 10% to 15% of all childhood brain stem tumors. These neoplasms have a distinct clinical presentation, distinct imaging characteristics, and a more favorable prognosis than diffuse brain stem gliomas. This article outlines the present management of cervicomedullary and dorsally exophytic neoplasms. Copyright (C) 2000 by W.B. Saunders Company.
Source: EMBASE

120. Glioma: Novel considerations and treatment modalities

Author(s) Tomera J.F.
Citation: Drugs of Today, June 2000, vol./is. 36/6(355-367), 0025-7656 (June 2000)
Publication Date: June 2000
Abstract: Glioma tumors often evade traditional cancer treatments and quickly invade healthy brain tissue. Current clinical perspective focuses on the invasiveness of glioma cells which follow distinct anatomic structures within the central nervous system. Advances in magnetic resonance imaging have made it the procedure of choice for identifying brainstem gliomas and classifying them anatomically. Etiologic considerations include adhesion, migration, invasiveness, cell proliferation, angiogenesis and neurotoxin release. This review examines various novel interventions used in treating these deadly growths to
prolong life. Recent interventional studies, detecting the cancer's unique characteristics, include the mechanisms that help it survive and spread throughout the brain. Current therapies include those that target glioma cells only, limit the spread of the cancer or block molecules which sustain the tumor. A variety of specific agents, general chemotherapy, radiotherapy and surgery are discussed. (C) 2000 Prous Science.

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121. A detrimental effect of a combined chemotherapy-radiotherapy approach in children with diffuse intrinsic brain stem gliomas?
Author(s) Freeman C.R., Kepner J., Kun L.E., Sanford R.A., Kadota R., Mandell L., Friedman H.
Citation: International Journal of Radiation Oncology Biology Physics, June 2000, vol./is. 47/3(561-564), 0360-3016 (01 Jun 2000)
Publication Date: June 2000
Abstract: Purpose: To compare the proportion of patients that survive at least 1 year following treatment with hyperfractionated radiotherapy (HRT) to a dose of 70.2 Gy on Pediatric Oncology Group (POG) study 8495 with that of patients treated with similar radiotherapy plus cisplatinum given by continuous infusion on weeks 1, 3, and 5 of radiotherapy on POG 9239. Methods and Materials: The eligibility criteria for the two studies were identical and included age 3 to 21 years, previously untreated tumor involving the brain stem of which two-thirds was in the pons, history less than 6 months, and clinical findings typical for diffuse intrinsic brain stem glioma, including cranial nerve deficits, long tract signs, and ataxia. The outcome of 57 patients who were treated at the 70.2 Gy dose level of POG 8495 between May 1986 and February 1988 was compared with that of 64 patients treated with identical radiotherapy plus cisplatinum on POG 9239 between June 1992 and March 1996. Results: The number of patients accrued to POG 9239 was determined to guarantee that the probability was at least 0.80 of correctly detecting that the 1-year survival rate exceeded that of patients on POG 8495 by 0.2. However, the z value for this test was -1.564, giving a p value of 0.9411. That is, there is almost sufficient evidence to conclude that survival for patients receiving HRT plus cisplatinum on POG 9239 was worse than that for patients receiving the same radiotherapy alone on POG 8495. Conclusion: The finding that patients who received cisplatinum given as a radiosensitizing agent concurrent with HRT fared less well than those receiving the same dose of HRT alone was unexpected and is clearly a cause for concern as many current protocols for patients with diffuse intrinsic brain stem gliomas call for use of chemotherapeutic and/or biological agents given concurrent with radiotherapy. (C) 2000 Elsevier Science Inc.
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122. Radiation therapy and high-dose tamoxifen in the treatment of patients with diffuse brainstem gliomas: Results of a Brazilian Cooperative Study
Author(s) Broniscer A., Da Costa Leite C., Lanchote V.L., Machado T.M.S., Cristofani L.M.
Citation: Journal of Clinical Oncology, March 2000, vol./is. 18/6(1246-1253), 0732-183X (March 2000)
Publication Date: March 2000
Abstract: Purpose: The efficacy of radiation therapy (RT) combined with tamoxifen (TX) was tested in patients diagnosed with diffuse brainstem gliomas in a multicenter trial. Patients and Methods: TX was administered orally (maintenance dose: 200
mg/m² per day) along with conventional local RT and then continued for 52 additional weeks. Survival, tumoral radiologic response, and toxicity were evaluated. Compliance was assessed using pharmacokinetic measurements. Results: Of 29 patients, 27 completed RT (median dose, 54 Gy). Of 22 assessable patients, 11 (50%) had an objective radiologic response. The mean TX steady-state serum level was 2.44 μmol/L +/- 1.02 μmol/L. Only three patients completed the entire course of treatment without tumoral progression or significant toxicity. Common side effects included nausea and vomiting. Hepatotoxicity (five patients), neurotoxicity (two patients), venous thrombosis (one patient), bilateral ovarian cysts (two patients), and transient neutropenia (one patient) were also observed. Median survival was 10.3 months. Only four patients remain alive without tumoral progression. The 1-year survival rate (mean +/- SD) was 37.0% +/- 9.5%. Conclusion: This treatment combination produced no significant change in the overall poor prognosis of these patients. Most tumors responded initially to treatment but recurred as the study progressed. A minority of patients seemed to benefit from the extended use of TX. Generally, treatment was well tolerated, with good patient compliance, but we recommend continuous close monitoring for side effects. Based on our poor results, we recommend that alternative treatments be tested in patients with this type of tumor. (C) 2000 by American Society of Clinical Oncology.

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123. Clinical management of brain stem glioma
Author(s) Walker D.A., Punt J.A.G., Sokal M.
Citation: Archives of Disease in Childhood, 1999, vol./is. 80/6(558-564), 0003-9888;1468-2044 (1999)
Publication Date: 1999
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124. A phase II study of KRN8602(MX2), a novel morpholino anthracycline derivative, in patients with recurrent malignant glioma
Author(s) Kuratsu J.-I., Arita N., Kurisu K., Uozumi T., Hayakawa T., Ushio Y.
Citation: Journal of Neuro-Oncology, 1999, vol./is. 42/2(177-181), 0167-594X (1999)
Publication Date: 1999
Abstract: KRN8602(MX2) is a newly developed morpholino-anthracycline that has been found to cross the blood-brain barrier and be distributed in brain tissue after intravenous administration and to be effective against human glioma cells and the intracerebrally transplanted tumors in vivo. In order to confirm these promising preclinical observations clinically, we performed a phase II trial of KRN8602 in patients with recurrent malignant glioma. The 44 patients enrolled received at least 2 cycles of KRN8602 35 mg/m²/day at 3-4 week intervals by intravenous bolus. Of the 44 patients, 37 could be evaluated for response, and 39 for toxicity. One patient with anaplastic astrocytoma had a complete response (1/37, 3%), and 2 patients with anaplastic astrocytoma and 1 with brain stem glioma had a partial response (3/37, 8%). The overall response rate was 11% (4/37). All patients who responded had received prior chemotherapy that included nitrosoureas. No response was observed in the patients with glioblastoma. Myelosuppression was moderately severe, with 72% of patients developing grade 3 or 4 leukopenia. Severe nausea/vomiting was observed in 31% of the patients. No severe cardiotoxicity was observed. The results indicate that KRN8602 has modest activity against recurrent malignant glioma with relatively severe, but manageable toxicity. It seems
to be worthwhile to further assess the efficacy and toxicity of KRN8602 against malignant glioma, which is generally less sensitive to chemotherapy.

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125. Diffuse brain stem gliomas: Are we improving outcome?

Author(s) Shuper A., Kornreich L., Loven D., Michowitz S., Schwartz M., Cohen I.J.

Citation: Child's Nervous System, October 1998, vol./is. 14/10(578-581), 0256-7040 (October 1998)

Publication Date: October 1998

Abstract: We reviewed our experience with diffuse brain stem glioma (dBSG) to evaluate whether any improvement of outcome had occurred in our patients over the years. Of the 24 children referred to our department with suspected dBSG from 1981 to 1997, 5 had a different final diagnosis based on the clinical course. Mean survival in the remainder was 16+/−9.8 months from diagnosis. Survival increased with a longer interval from onset of symptoms to diagnosis (12.9+/−9.0 months with an interval of 1-4 weeks; 19.50+/−10.8 months with a longer interval). Visual symptoms at presentation were associated with a poorer prognosis. Survival was better in the 3- to 5-year age group (at diagnosis). Overall, a trend toward a slight improvement in survival was seen over the years, which we presumptively attribute to the introduction of intensive chemotherapy for these patients. We suggest that chemotherapy may be important in the management of dBSG until a better modality is found.

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126. A phase II clinical trial of idarubicin administered to children with relapsed brain tumors

Author(s) Arndt C.A.S., Krailo M.D., Steinherz L., Scheithauer B., Liu-Mares W., Reaman G.H.

Citation: Cancer, August 1998, vol./is. 83/4(813-816), 0008-543X (15 Aug 1998)

Publication Date: August 1998

Abstract: BACKGROUND. Idarubicin (IDR), an anthracycline that is a derivative of daunorubicin, was synthesized in an attempt to find new analogs of daunorubicin with an improved spectrum of activity and diminished acute or chronic toxicity. Because of the favorable pharmacokinetic profile of IDR (with the persistence of its active metabolite [idarubicinol], the penetration of idarubicinol into the cerebrospinal fluid, and the lipophilicity of IDR/idarubicinol compared with other anthracyclines), its more favorable therapeutic index regarding cardiotoxicity in animals, and its potential for oral administration, a Phase II trial of IDR in children with relapsed brain tumors was undertaken. METHODS. Patients received IDR at a dose of 5 mg/m<sup>2</sup>/day x 3 days by intravenous bolus, followed by granulocyte-colony stimulating factor (G-CSF) at a dose of 5 μg/kg/day, starting on Day 7 of each cycle and continuing for at least 7 days, until the absolute neutrophil count was <=10,000/mm<sup>3</sup>. RESULTS. Three of 19 patients with high grade astrocytoma achieved a partial response, 1 of 20 patients with medulloblastoma had a complete response, and 0 of 13 patients with ependymoma and 0 of 13 patients with brainstem tumors had responses. In nine other brain tumor patients there were no responses. The most significant toxicity was myelosuppression. CONCLUSIONS. IDR, given at a dose of 5 mg/m<sup>2</sup>/day x 3 days, is not sufficiently active against relapsed medulloblastoma, ependymoma, or brain stem tumors to warrant further study of this agent in a Phase III setting. The response rate for patients with relapsed high grade astrocytoma was 15% (95% confidence interval, 3.3-40%).

Source: EMBASE
127. Pediatric brain stem gliomas: A review

Author(s): Freeman C.R., Farmer J.-P.

Citation: International Journal of Radiation Oncology Biology Physics, January 1998, vol./is. 40/2(265-271), 0360-3016 (15 Jan 1998)

Publication Date: January 1998

Abstract: Tumors arising in the brain stem, comprising the midbrain, pons, and medulla oblongata, are now recognized as distinct clinico-pathological entities. Advances in neurosurgical techniques have made surgery not only feasible but the treatment of choice for some of these tumor types. Previously the mainstay of treatment, radiotherapy is now used more selectively. This article reviews the current state of knowledge with regard to tumors arising in the brain stem, the therapeutic options available for each, and provides recommendations with regard to management.

Source: EMBASE

128. Brainstem gliomas

Author(s): Hoffman H.J.

Citation: Clinical neurosurgery, 1997, vol./is. 44/(549-558), 0069-4827 (1997)

Publication Date: 1997

Source: EMBASE

129. Carboplatin and etoposide with hyperfractionated radiotherapy in children with newly diagnosed diffuse pontine gliomas: A phase I/II study

Author(s): Walter A.W., Gajjar A., Ochs J.S., Langston J.W., Sanford R.A., Kun L.E., Heideman R.

Citation: Medical and Pediatric Oncology, 1997, vol./is. 30/1(28-33), 0098-1532 (1997)

Publication Date: 1997

Abstract: Background. Diffuse pontine gliomas remain one of the most lethal of pediatric malignancies despite the use of increasingly intensive therapies. We delivered intensive chemotherapy during and following 70.2 Gy of hyperfractionated radiation therapy in an attempt to improve survival. Procedure. Nine consecutive children with diffuse pontine gliomas were treated on this single arm study. Carboplatin, given in combination with fixed dose etoposide, was escalated in successive cohorts to determine its maximum tolerated systemic exposure (AUC). Outcome was coded based on imaging characteristics and clinical status. Results. Eight of the nine children on this study died of their disease at a median of 44 weeks, essentially the same survival as those treated on a previous Pediatric Oncology Group study using hyperfractionated radiation therapy alone. Toxicity was almost exclusively hematologic and not associated with significant morbidity. Conclusions. The use of concurrent carboplatin and etoposide with hyperfractionated radiation therapy did not appear to improve the survival in this group of children with diffuse pontine gliomas. The toxicity of this chemotherapy during radiation therapy was primarily hematologic and well tolerated. New approaches to the treatment of these tumors need to be investigated.

Source: EMBASE
130. Focal midbrain glioma: Long term survival in a cohort of 16 patients and the implications for management

Author(s) Hamilton M.G., Lauryssen C., Hagen N.

Citation: Canadian Journal of Neurological Sciences, 1996, vol./is. 23/3(204-207), 0317-1671 (1996)

Publication Date: 1996

Abstract: Background: Focal gliomas involving the midbrain tectum and tegmentum have been identified as having a better prognosis than diffuse tumors affecting the brain stem. However, only limited information is available concerning treatment effectiveness and long term outcome for these patients. Methods: A retrospective, population-based cancer registry survey was performed to assess the clinical features and treatment courses of patients with focal midbrain tumors. Results: Sixteen patients with midbrain gliomas were identified; eight had tectal gliomas and eight tegmental gliomas. Thirteen patients presented with symptoms related to hydrocephalus, and 12 required a ventriculoperitoneal shunt. Seven patients underwent surgery directed at the tumor. Eight patients underwent initial radiation therapy and none had initial chemotherapy. One patient diagnosed at age 18 months had a rapidly growing tumor after 14 months of follow up which has responded to chemotherapy. The mean survival of this patient population was 84 months (range 3-280 months) after diagnosis, with only one tumor related death occurring (280 months after diagnosis). Survival was not affected by tumor location within the midbrain (tegmental or tectal) or by whether radiation therapy was or was not administered. Conclusions: Patients with focal midbrain gliomas require symptom control aimed at treatment of hydrocephalus, or mass effect from the tumor. However the extended survival of this population suggests that routine-aggressive surgical debulking is often not required. Furthermore, the routine use of radiation therapy or chemotherapy for all such patients is questioned.

Source: EMBASE

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131. Contemporary chemotherapy issues for children with brainstem gliomas

Author(s) Allen J.C., Siffert J.

Citation: Pediatric Neurosurgery, February 1996, vol./is. 24/2(98-102), 1016-2291 (February 1996)

Publication Date: February 1996

Abstract: Radiotherapy has remained the mainstay of treatment for children with intrinsic, diffuse pontine tumors in spite of over 20 years of clinical trials attempting to validate the additional role of chemotherapy. Conventional phase II clinical trials conducted in patients with recurrent or progressive brainstem gliomas using single chemotherapy agents such as cyclophosphamide, carboplatin, cisplatin, etoposide and thiotepa or combinations of chemotherapy agents have produced low response rates in the range of 15-20%. Preradiotherapy chemotherapy phase II trials in newly diagnosed patients have yielded similar results with a therapeutic window as long as 4 months. Preliminary data from protocols employing high-dose chemotherapy with stem cell support have also met with disappointment. The one published phase III trial conducted by the Children's Cancer Study Group comparing radiotherapy with radiotherapy plus chemotherapy (CCNU, vincristine and prednisone) failed to establish a benefit to multimodality therapy. Current studies include the use of radiosensitizing chemotherapy (carboplatin, estramustine and cisplatin) in newly diagnosed patients and more intensive neoadjuvant chemotherapy trials. Major advances in our management await insights into molecular vulnerability of high-grade gliomas.

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132. Strategies in the treatment of diffuse pontine gliomas: The therapeutic role of hyperfractionated radiotherapy and chemotherapy

**Author(s)** Jennings M.T., Freeman M.L., Murray M.J.

**Citation:** Journal of Neuro-Oncology, 1996, vol./is. 28/2-3(207-222), 0167-594X (1996)

**Publication Date:** 1996

**Abstract:** This article will review the current treatment of pediatric patients with diffuse pontine gliomas (DPG) and discuss three potential avenues of therapeutic research including (i) radiotherapy (RT) in combination with radiation sensitizers, (ii) dose-intensive, induction chemotherapy with hematopoietic support followed in sequence with RT applied as a 'consolidation' therapy, and (iii) the interleaved application of phase-specific chemotherapeutic agents and hyperfractionated external beam radiotherapy (HFEBRT) referred to as 'chemoradiotherapy'.

**Source:** EMBASE

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133. Surgical indication and technical considerations in the management of benign brain stem gliomas

**Author(s)** Constantini S., Epstein F.

**Citation:** Journal of Neuro-Oncology, 1996, vol./is. 28/2-3(193-205), 0167-594X (1996)

**Publication Date:** 1996

**Abstract:** The treatment of brain stem gliomas has evolved over the last few decades, reflecting advances in imaging (MR), microsurgical techniques and biological understanding. The aim of this chapter is to provide a preoperative classification for intrinsic brain stem lesions that will predict histopathology and biological behavior from the clinical syndrome and the MR appearance. Such a classification system may help selecting children with brain stem tumors that can benefit from surgery. Technical considerations, potential surgical complications, and the ways to avoid them are discussed.

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134. Long term survivors of childhood brain stem gliomas treated with hyperfractionated radiotherapy: Clinical characteristics and treatment related toxicities

**Author(s)** Freeman C.R., Bourgouin P.M., Sanford R.A., Cohen M.E., Friedman H.S., Kun L.E.

**Citation:** Cancer, February 1996, vol./is. 77/3(555-562), 0008-543X (01 Feb 1996)

**Publication Date:** February 1996

**Abstract:** BACKGROUND. Over the past decade, the principal focus of research in pediatric brain stem gliomas has been on the use of hyperfractionated radiotherapy (HRT). The purpose of this study was to evaluate the clinical characteristics and treatment related toxicities of long term survivors of HRT treatment. METHODS. Of the 130 children with brain stem tumors treated with escalating doses of HRT on Pediatric Oncology Group (POG) 8495, there are only 9 long term survivors. Prospectively collected data, including flow sheets and all pretreatment and follow-up radiologic studies, were reviewed for these patients. Additional information was requested from the treating institutions with regard to sequelae of treatment. RESULTS. Clinical characteristics (including age, sex, duration of symptoms, and presenting signs) for the nine surviving patients were not different from the total population of patients treated on POG 8495. Pretreatment imaging, however, revealed that only four of the nine patients had typical diffuse intrinsic pontine lesions and,
conversely, that at least three of the nine patients had lesions that would now be considered relatively favorable. Complete information regarding treatment related toxicity was available for eight patients, only one of whom is without sequelae. Seven have schooling difficulties, two have a seizure disorder, five have hearing loss, and two have required growth hormone replacement. Follow-up imaging findings were striking in four of the eight patients because of white matter changes consistent with leukoencephalopathy (two patients), diffuse microhemorrhages (one patient), and dystrophic calcification (one patient) in the radiation field. CONCLUSIONS. The high frequency of treatment related sequelae in long term survivors of HRT suggests a need for caution in the use of HRT, particularly in patients who have brain stem tumors with a more favorable prognosis.

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135. Outcome of children with brain stem gliomas after treatment with 7800 cGy of hyperfractionated radiotherapy: A Childrens Cancer Group Phase I/II trial


Citation: Cancer, 1994, vol./is. 74/6(1827-1834), 0008-543X (1994)

Publication Date: 1994

Abstract: Background. Brain stem gliomas remain the childhood brain tumors most resistant to treatment. Treatments with hyperfractionated radiotherapy at doses as high as 7560 cGy have been fairly well tolerated. This study was undertaken to determine the toxicity and possible efficacy of hyperfractionated radiotherapy in children with brain stem gliomas using 100 cGy of radiation twice daily, to a total dose of 7800 cGy. Methods. Sixty-six children (mean age at diagnosis, 7.5 years) with diffuse intrinsic brain stem gliomas were treated. Patients were evaluated for potential toxicity of treatment, progression-free survival, survival, and response to treatment. Results. Objective response to treatment was documented in 20 of 58 (34%) evaluable patients, with 8 (14%) patients having a greater than 50% reduction in tumor size. Overall survival was 35% plus or minus 6% at 1 year and 11% plus or minus 6% at 3 years. Intralesional cystic/necrotic radiographic changes developed in nine patients 6 weeks after radiation, and three of these patients subsequently improved without antitumor intervention. Six of 14 autopsied patients had evidence of probable radiation-induced intralesional necrotic damage, and in 1, necrosis may have played a role in death. Thirty-three of 66 patients were treated with steroids for prolonged periods. Conclusions. The results of this treatment regimen demonstrate that hyperfractionated radiotherapy, as delivered in this study to a total dose of 7800 cGy, is relatively well tolerated, but may result in prolonged steroid- use dependency and possible radiation-associated damage. Objective responses to treatment were seen in 34% of patients, but these results were not better than those seen at lower doses of hyperfractionated radiotherapy. There is no evidence that radiation to 7800 cGy results in improved survival for patients with diffuse intrinsic brain stem gliomas.

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136. High-dose chemotherapy with marrow reinfusion and hyperfractionated irradiation for children with high-risk brain tumors

Author(s) Kedar A., Maria B.L., Graham-Pole J., Ringdahl D.M., Quisling R.G., Mickle J.P., Mendenhall N.P., Marcus Jr. R.B., Gross S.

Citation: Medical and Pediatric Oncology, 1994, vol./is. 23/5(428-436), 0098-1532 (1994)

Publication Date: 1994

Abstract: Between November 1990 and March 1993, nine pediatric patients with newly diagnosed brain tumors having a high risk of failure with standard treatment received high-dose thiotepa/cyclophosphamide chemotherapy followed by autologous bone marrow
infusion and involved-field hyperfractionated radiation therapy. The presenting diagnoses were brainstem glioma (BSG) [6], parietal mixed high-grade oligodendroglioma-astrocytoma [1], thalamic anaplastic astrocytoma [1], and high-grade parietal glioma [1]. Following chemotherapy there were two partial responses, one minor response, three with stable disease, and one with progressive disease. Responses were not evaluated in two patients who had toxic deaths. Following radiation two patients, one with brainstem glioma and one with anaplastic mixed glioma, achieved complete remission. The overall survival is no better than conventional therapy.

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137. Pediatric glial neoplasms including brain-stem gliomas

Author(s) Packer R.J., Vezina G.
Citation: Seminars in Oncology, 1994, vol./is. 21/2(260-272), 0093-7754 (1994)
Publication Date: 1994
Source: EMBASE
Available in print at ULHT journal article requests. Complete the online form to obtain articles.

138. Brainstem gliomas

Author(s) Packer R.J., Nicholson H.S., Vezina L.G., Johnson D.L.
Citation: Neurosurgery clinics of North America, October 1992, vol./is. 3/4(863-879), 1042-3680 (Oct 1992)
Publication Date: October 1992
Abstract: Brainstem gliomas, a relatively common form of childhood brain tumor, are highly resistant to therapy. With computed tomography and magnetic resonance imaging, these lesions can be diagnosed with a high degree of reliability. The indications for surgery are unclear. Focal lesions may be amenable to partial resections. Stereotactic approaches can be used for diffuse lesions, but it has not been shown that the information obtained changes the approach to treatment or outcome. Higher dose radiotherapy has been recently used but has not improved survival for most patients. Patients with brainstem gliomas must be stratified into risk groups, and new means of treatment are needed.

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... 2; occipitoparietal, 1; thalamus, 1; pineal, 1; spinal, 2; brain stem with temporal ... of the
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