

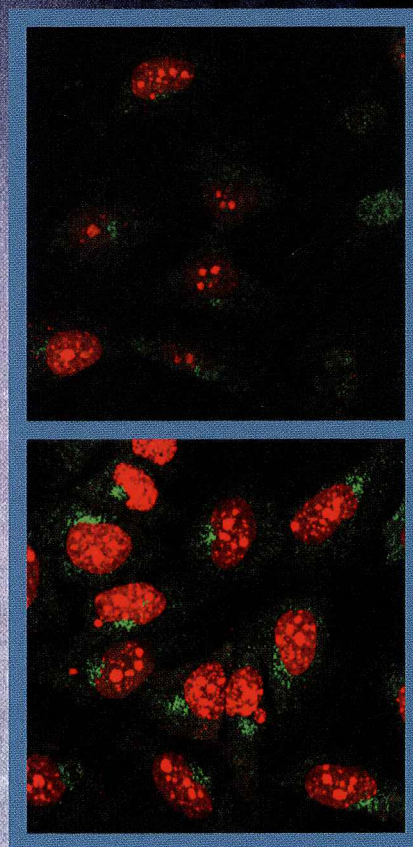
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Editorial

Letter to the Editor

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PE-04. VASCULARITY IN PEDIATRIC INTRACRANIAL EPENDYMOMA

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Ependymomas are the third most common brain tumor in the pediatric population. The main challenges in ependymoma treatment are the lack of markers predicting tumor behavior and the limited treatment options, especially in cases of recurrent disease. Radiation is the mainstay of treatment, and adjuvant chemotherapy has thus far not improved survival rates. This study evaluated microvessel density (MD) and angiogenic features as potential independent markers of outcome and to establish a basis for antiangiogenic therapy. Patients with a pathologic diagnosis of intracranial ependymoma who underwent surgery at the Hospital for Sick Children in Toronto between 1985 and 2004 were retrospectively identified through the pathology and oncology databases. For each patient, all pathologic blocks and corresponding slides were obtained and reviewed for diagnostic accuracy and tissue adequacy. Ependymoma tissue microarrays were constructed and immunostained with factor VIII and specimens were evaluated for MD. Kaplan-Meier analysis was used to look for an effect on progression-free survival (PFS). Cox regression was used for multivariate analysis. Seventy-five patients were identified with sufficient clinical data and adequate pathological material. The mean age at presentation was 5.8 years +/- 0.5 years. Forty patients (53%) had at least 1 recurrence, including 29 who had at least a second sample available for MD comparison between the time of diagnosis and the time of recurrence. The 5-year overall survival rate was 57% +/- 7% (10-year OS rate, 38% +/- 9%) and the 5-year PFS rate was 34% +/- 6% (10-year PFS rate, 30% +/- 7%). MD showed a median of 16 vessels/1.2 mm² with a wide range of variation (SD, 11). No differences in MD were observed between classic (N = 29) versus anaplastic (N = 46) ependymomas (median, 17 vessels/1.2 mm² for both) and between tissue acquired at the time of initial diagnosis versus at recurrence (median, 16 vessels/1.2 mm² for both). We did not find any correlation between age and MD. There was a trend toward longer PFS in those patients with low MD (< 16 vessels/1.2 mm²) at the time of initial diagnosis (P = 0.073), which was significant in those patients over the age of 3 years (P = 0.011). MD in recurrent tumors was not informative. Low MD is predictive of longer PFS in children older than 3 years at the time of their initial ependymoma diagnosis, independent of tumor grade and extent of surgical resection. Evaluation of angiogenic features in these tumors may identify a subgroup amenable to antiangiogenic therapy.

PE-05. TREATMENT OF MULTICENTRIC BRAINSTEM GLIOMAS WITH ANTINEOPLASTONS (ANP) A10 AND AS2-1
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Antineoplastons (ANP) are synthetic analogues of naturally occurring phenylacetylglutamine, phenylacetylglutamine, and phenylacetate. Previous reports have described a significant percentage of objective responses and increased overall survival rates in patients with newly diagnosed and recurrent diffuse intrinsic brainstem gliomas and multicentric gliomas. This study describes the treatment of a group of patients involved in phase II trials of ANPs who had both brainstem gliomas and multicentric tumors (MBSG). These trials were monitored by the FDA and the Institutional Review Board. Nineteen evaluable patients diagnosed with MBSG were treated with ANP. The median age was 9.2 years (range, 3.9–40.8 years) and 90% were less than 18 years old. Diffuse intrinsic brain stem glioma was diagnosed in 95% of patients and cervicomedullary tumor in 5%. A biopsy was performed in 37% of patients, and pathology results confirmed 4 with low-grade and 3 with high-grade gliomas. Tumor recurrence after previous standard treatment was documented in 60% of patients. ANP was given intravenously daily through a subclavian venous catheter and a double-channel infusion pump. The median duration of i.v. ANP was 4½ months, and the median of average dosages of A10 was 9.2 g/kg/day and AS2-1 was 0.32 g/kg/day. Responses were assessed using gadolinium-enhanced MRI scans and confirmed using PET scans in some cases. A complete response (CR) was determined in 11%, partial response (PR) in 5%, stable disease (SD) in 37%, and progressive disease (PD) in 47%. The overall survival rate (OS) at 1 year was 53%, at 2 years was 32%, and at 5 years was 16%. The progression-free survival rate (PFS) was 26% at 1 year and 16% at 2 years. The maximum survival time is 9+ years. The patients did not experience any serious toxicities (grades III-IV), and there were no chronic toxicities. The results of the study showed favorable responses and survival data in a small group of patients diagnosed with difficult-to-treat brain tumors.

PE-06. THE EFFICACY OF RADIOSURGERY IN CHILDREN WITH MEDULLOBLASTOMA

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Medulloblastoma is the most common primary central nervous system tumor that arises in childhood. There is strong evidence that medulloblastoma is very difficult to control, despite the use of radiation and chemotherapy. Children who undergo surgical resection have a higher overall rate of survival. The evolution of stereotactic radiosurgery (SRS) may offer hope for patients with medulloblastoma. The objective of this study was to determine the efficacy of SRS compared with surgery for patients with medulloblastoma. We searched 3 electronic databases: the Cochrane Central Register of Controlled Trials (CENTRAL, 2004 issue 2), MEDLINE (1966 to present), and EMBASE (1974 to present). Comparative studies that assessed the efficacy of SRS in children with medulloblastoma were included. Outcome measures included progression-free survival (PFS), overall survival, and tumor recurrence. Despite extensive searching, no randomized controlled trials (RCT) were found. The electronic search identified 27 studies. A total of 15 studies were selected for further evaluation. Seven articles met eligibility criteria and were included in the final review (N = 144). The weighted mean for the PFS median was 10.7 months (95% confidence interval [CI], 9.4–12 months), and the weighted mean for overall PFS and survival at a minimum of a 2-year follow-up was 16.8% (95% CI, -4.7%–81.2%) and 39.0% (95% CI, 6.3%–71.8%), respectively. The rate of tumor recurrence was 29.8% (95% CI, -0.1–59.8). SRS appears to reduce the proportion of first failures occurring locally and is associated with better outcome when implemented as a part of initial treatment. Some patients with unresectable relapsed disease benefit from SRS; however, SRS treatment for multiple lesions does not appear to be curative. Local recurrence can be controlled by SRS with chemotherapy but the survival of patients with metastases may not be prolonged effectively by SRS in conjunction with aggressive chemotherapy. A limitation in the literature is the lack of RCTs. Cohort or single-arm studies only provide partial information and have the risk of significant bias. An appropriate RCT should be designed to determine which technique is superior for patients with medulloblastoma. The treatment of medulloblastoma with SRS, either alone or in combination, merits further investigation before clear recommendations can be made.

PE-07. FLOW CYTOMETRIC ANALYSIS OF NEURAL STEM CELL MARKERS ON PEDIATRIC BRAIN TUMORS

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The recent identification of neuroepithelial stem cells (NSC) in human fetal tissue has led to the opportunity to determine the relationship of these cells to brain tumor cells. To better understand the relationship between pediatric tumors and normal neural progenitors, we prospectively determined the frequency of tumor cells expressing NSC-associated cell surface proteins in a series of pediatric brain tumor specimens. Brain tumors isolated from pediatric patients were dissociated, and isolated cells were then stained with monoclonal antibodies specific for cell surface molecules. The markers that we analyzed included CD133, CD24, and CD45. The cells were analyzed using Becton Dickinson FACSDiva flow cytometry software (Becton Dickinson Biosciences, NJ). Fifteen pediatric tumors were analyzed, including 4 medulloblastomas, 2 ependymomas, 2 pilocytic astrocytomas, and 1 each of the following tumors: low-grade glioma (WHO II), anaplastic astrocytoma, atypical teratoid rhabdoid tumor (ATRT), astroblastoma, malignant teratoma, ganglioglioma, and nongerm-cell germinoma. CD133 was expressed in all 9 high-grade (WHO III or IV) tumors with an average of 14.7% (SD, 18.5%). We found no detectable expression of CD133 in 5 low-grade tumors (WHO I or II). One ependymoma (WHO II) had 41% CD133 expression. In 6 cases, the staining results enabled us to determine the frequency of cells expressing the specific NSC phenotype (CD133+/CD24-/CD34-/CD45-). An astroblastoma, an ATRT, and a malignant teratoma contained 24%, 1.4%, and 0.22% CD133+/CD24-/CD34-/CD45- cells, respectively. Two pilocytic astrocytomas and 1 nongerm-cell germinoma failed to express the NSC phenotype. In this series, high-grade pediatric tumors expressed higher levels of CD133 than low-grade tumors. Furthermore, some tumors contained cells expressing the full pattern of cell surface proteins established for normal fetal NSC. These results suggest a potential relationship between normal progenitor cells and neuro-oncogenesis and highlight the possible significance of CD133 expression and tumor anaplasia.