The review by Gururangan and Friedman takes an interesting and informative approach to pediatric brain tumors in emphasizing the possible biologic bases for chemotherapy failure in these neoplasms in general, and focusing on newer, as yet largely unproven, strategies employing "biologic" therapies to circumvent such mechanisms of tumor resistance. Many of these newer treatment strategies are drawn from the work of the authors and others in the field of adult malignant gliomas. To date, minimal progress has been achieved in improving outcome for children with malignant supratentorial gliomas and brainstem tumors. Hopefully, these new strategies will have significant benefit in pediatric as well as adult patients. However, we find that the authors have been inordinately pessimistic in presenting the achievements of their pediatric oncology colleagues in utilizing conventional chemotherapy strategies, particularly in the treatment of medulloblastoma, other primitive neuroectodermal tumors (PNET), and ependymoma.

**Standard-Risk Medulloblastoma**

The use of radiation therapy alone, at least for children and adolescents, is no longer accepted as the standard of treatment for patients with nondisseminated medulloblastoma. Historically, 5-year event-free survival rates, even in the modern era of carefully staged patients, have not exceeded 55% to 60%. Survival in children receiving traditional doses of 3,600 cGy to the neuraxis is also associated with well-documented permanent cognitive deficits. The most recent published studies in children and adolescents receiving the now-standard dose of 2,340 cGy to the neuraxis with chemotherapy, are reporting 5-year event-free survival rates in excess of 75% with some sparing of cognitive function. The recently opened Children's Oncology Group (COG) trial for these patients will assess the efficacy of a further reduction in radiation dose to the neuraxis as well as reduction in the extent of the radiation field (posterior fossa vs original tumor bed), in hopes of further preserving cognitive function. Not discussed by Gururangan and Friedman, but of paramount importance if we are indeed to improve...
cognitive functioning in survivors of medulloblastoma, is a greater understanding of the cause and thereby prevention of the postoperative posterior fossa syndrome. Also called akinetic mutism, this syndrome may have lasting effects on intellectual functioning more devastating than currently utilized irradiation doses. **High-Risk Medulloblastoma and Supratentorial PNET**

The benefits of adjuvant chemotherapy added to irradiation in children and adolescents with disseminated medulloblastoma and with any stage of supratentorial PNET are indisputable. Historically, children with disseminated medulloblastoma treated with conventional radiotherapy without adjuvant chemotherapy had zero survival.\[6\] Publications over the past decade, utilizing full-dose irradiation and adjuvant chemotherapy, have produced 3-year survival rates ranging from 50% to 60%. Likewise, patients with supratentorial pineal region PNET (pineoblastoma) and other supratentorial PNET achieve 3-year event-free survival rates as high as 60% to 75%, depending upon the extent of disease at diagnosis.\[7,8\] Indeed, contrary to Gururangan and Friedman's contention, it is not clear that their strategy of employing myeloablative chemotherapy with stem cell rescue for newly diagnosed pineoblastoma has improved survival over the best-reported conventional regimens. **Ependymoma**

The lack of benefit produced by chemotherapy is less persuasive than Gururangan and Friedman have indicated. In a multi-institution pilot some years ago, Needle et al indicated that patients with incompletely resected tumor who received an ifosfamide (Ifex) and platinum-based chemotherapy regimen fared almost as well as patients with completely resected tumor, all of whom received irradiation as well.\[9\] This suggested that chemotherapy could improve an otherwise poor result from irradiation alone for incompletely resected patients, while not improving an already more favorable outcome for completely resected patients treated with irradiation alone. Furthermore, the most recent analyses of the Children's Cancer Group (CCG) trial for ependymoma—a large experience with longer follow-up—confirm and expand on the Needle findings: Children with incomplete resections who received preirradiation chemotherapy enjoyed a 3-year event-free survival equivalent to that of children with complete resection treated with irradiation only. Additionally, a beneficial role for chemotherapy in ependymoma is seen in studies of ependymoma in young children (< 3 years of age), in which attempts to avoid irradiation with intensive chemotherapy, either with[10] or without (UK-CCG) marrow ablative chemotherapy and stem cell rescue, produced 5-year event-free survivals either superior to or equivalent to other infant ependymoma studies utilizing chemotherapy and irradiation (eg, CCG-921, the German HIT study). **Role of Biologic Agents**

Clearly, much work lies ahead in improving the treatment of pediatric brain tumors. The authors briefly refer to advances made in identifying molecular markers in medulloblastoma. However, the work done on medulloblastoma needs to be expanded to identify molecular risk groups in all brain tumor patients using various technologies. The technologies used in identifying these molecular markers should include genomic markers (single nucleotide polymorphism [SNP] arrays of host and tumor), transcriptome markers (RNA arrays), and proteome markers (tissue microarrays, histologic evaluation). The COG recently initiated such an endeavor for its brain tumor trials and plans to utilize some of these technologies. Identification of these markers will lead to molecularly based risk classifications. These markers may also serve as potential targets, as noted by the authors. The combinations of these markers—especially the SNP information—may further facilitate our understanding of host-drug (pharmacodynamics/pharmacokinetics) and tumor-drug (drug resistance) interactions. Use of biologic agents as therapies without accurate molecular classification of patients may lead to inaccurate assessment of their efficacy, as was seen in the recent trial of the epidermal growth factor receptor tyrosine kinase inhibitor gefitinib (Iressa) in non-small-cell lung cancer.\[11\] The initial trials with antiangiogenic therapies, starting in the early 1990s, have been disappointing. Only recent phase III data on bevacizumab (Avastin), which showed efficacy in large adult trials requiring hundreds of patients with metastatic cancer, allowed the assessment of this agent's efficacy.\[12\] Pediatric brain tumor trials with such large numbers of patients are not feasible. Therefore, we must improve our preclinical and clinical tools used in combinatorial drug selection, efficacy evaluation, and side-effect prediction. Only
when armed with preclinical brain tumor models that correlate with survival and in vivo surrogate markers that assess tumor response can we fully evaluate the potential of biologic agents in our molecularly profiled patients.

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