Diagnostic and Therapeutic Stratification of Childhood Brain Tumors: Implications for Translational Research
Ian F. Pollack
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Recent advances in the categorization of childhood brain tumors have improved risk-based treatment planning. In several instances, new therapeutic strategies that incorporate these advances have resulted in meaningful improvements in progression-free and overall survival. Current studies are directed at further refining therapy based on clinical, biological, and molecular data; testing the effectiveness of a number of novel therapeutic strategies for high-risk tumors; and examining approaches to reduce sequelae of treatment among more favorable-risk tumor subsets. Because multiple tumor subtypes are individually relatively uncommon, most such studies are being conducted by large co-operative groups, such as the Children’s Oncology Group, or by smaller brain tumor-focused consortia, such as the Pediatric Brain Tumor Consortium.

Keywords: brain tumor; pediatric; molecular marker; prognostic factor

Medulloblastoma/Primitive Neuroectodermal Tumors

Primitive neuroectodermal tumors, such as medulloblastoma, pineoblastoma, and supratentorial primitive neuroectodermal tumors, are the most common childhood malignant brain tumors. On the basis of studies in the 1980s and 1990s, these tumors are generally subdivided into average-risk and high-risk groups, reflecting differences in prognosis following treatment with standard doses of irradiation (approximately 3600 cGy to the craniospinal axis with a boost to a dose of 5400 cGy to the tumor bed).4-6 The 5-year progression-free survival rate of patients with average-risk tumors (eg, extensively resected, nonmetastatic (M0) posterior fossa lesions in children older than 3 years) was approximately 60%, whereas the survival rate of patients with high-risk tumors (eg, those with extensive residual disease, metastases, or nonposterior fossa tumor location, and those diagnosed in children younger than 3 years) was less than 40%.4-6 These observations led to efforts to stratify therapy based on clinical risk factors, with the goal of improving survival in the high-risk group and reducing the sequelae of therapy in the average-risk group.7-9 In average-risk patients,
combining adjuvant chemotherapy with reduced doses of radiotherapy to decrease radiation-related cognitive and endocrine toxicity was associated with high rates of long-term survival with potentially fewer sequelae than treatment with standard doses of irradiation alone.7

To follow up on these observations, the Children’s Oncology Group initiated a randomized phase 3 study (A9961) that was designed to compare 2 adjuvant chemotherapy regimens for average-risk patients. This study validated the safety of reducing the dosage of craniospinal irradiation from 3600 to 2340 cGy in conjunction with chemotherapy. Because 5-year survival was greater than 80% with both regimens,7 an ongoing study (ACNS0331) is examining whether doses and volumes of irradiation can be further reduced with intensification of adjuvant chemotherapy. This study incorporates a 2-stage (factorial) randomized design. In children younger than 8 years, who have the most to gain from radiotherapy reduction, the study is evaluating the feasibility of further reducing the craniospinal radiotherapy dose from 2340 to 1800 cGy to diminish cognitive sequelae, and is examining the safety of decreasing the volume of posterior fossa irradiation using conformal delivery to decrease ototoxicity. In children 8 years and older, a single randomization for the boost volume size is incorporated. This study includes a panel of correlative analyses to evaluate molecular features such as TrkC, ErbB2, c-myc, and multigene expression profiles that have been found in recent retrospective studies to identify prognostically distinct tumor subsets independent of clinical factors.10-16 The prospective evaluation of these markers in the ACNS0331 study will be coupled with genome-wide screening of copy number alterations to look for patterns of gene losses and gains. Together, these studies are designed to identify molecular markers that can detect tumors likely to recur despite favorable clinical features, which would constitute a basis for biologically based stratification in future studies. Because a recent review of the data from A9961 demonstrated that the subset of tumors with anaplastic histological features was associated with a significantly worse prognosis than those with classical histology, independent of clinical risk factors, anaplastic tumors are now grouped with other high-risk primitive neuroectodermal tumors’ on current treatment protocols.

In parallel to the above strategies for average-risk medulloblastomas, which focus on maintaining favorable outcomes while reducing treatment-related sequelae, study design for high-risk primitive neuroectodermal tumors has been directed at increasing the percentage of children who achieve long-term survival.8,17,18 Recent approaches have built upon the known activity of both irradiation and chemotherapy for these tumors by administering conventional chemotherapeutic agents with radiosensitizing properties during irradiation, in conjunction with conventional postirradiation therapy. The recently completed Children’s Cancer Group-99701 study, which examined escalating doses of carboplatin with vincristine during radiotherapy followed by adjuvant chemotherapy after irradiation, achieved long-term survival rates that

### Table 1. Selected Molecular Targets in Current Children’s Oncology Group Trials

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medulloblastoma</td>
<td>TrkC, ErbB2, c-myc, expression profile, whole-genome allelotyping analysis</td>
</tr>
<tr>
<td>High-grade glioma</td>
<td>MGMT, p53, MB-1, expression profile, whole-genome allelotyping analysis</td>
</tr>
<tr>
<td>Low-grade glioma</td>
<td>MB-1, expression profile, whole-genome allelotyping analysis</td>
</tr>
<tr>
<td>Ependymoma</td>
<td>Expression profile, whole-genome allelotyping analysis</td>
</tr>
<tr>
<td>Germ cell tumors</td>
<td>Beta-HCG, AFP, expression profile, whole-genome allelotyping analysis</td>
</tr>
<tr>
<td>Infant tumors</td>
<td>INI1, TrkC, ErbB2, c-myc, expression profile, whole-genome allelotyping analysis</td>
</tr>
</tbody>
</table>

Abbreviations: AFP, alpha-fetoprotein; beta-HCG, beta human chorionic gonadotropin; MGMT, methylguanine-DNA-methyltransferase.

### Table 2. Molecularly Targeted Therapies Being Examined for Pediatric Brain Tumors

<table>
<thead>
<tr>
<th>Inhibitors of growth factor receptors</th>
<th>Modulators of drug resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDGFR inhibition</td>
<td>AGT inhibition</td>
</tr>
<tr>
<td>Imatinib</td>
<td>O’-Benzyguanine</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>PARP inhibition</td>
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<tr>
<td>AZD2171</td>
<td>INO-1001</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>HDAC inhibition</td>
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<tr>
<td>EGFR inhibition</td>
<td>SAHA</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>Depsipeptide</td>
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<tr>
<td>Erlotinib</td>
<td>Valproic acid</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>Inhibitors of angiogenesis</td>
</tr>
<tr>
<td>HER2 inhibition</td>
<td>VEGFR/multitargeted kinase inhibition</td>
</tr>
</tbody>
</table>

*Abbreviations: AGT, O’-alkylguanine-DNA alkyltransferase; Cox-2, cyclooxygenase-2; EGFR, epidermal growth factor receptor; HDAC, histone deacetylase; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; PARP, poly(ADP-ribose)/polymerase; PI3K, phosphatidylinositol 3-kinase; PDGFR, platelet-derived growth factor receptor; SAHA, suberoylanilide hydroxamic acid; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.*
appear to be superior to those from previous studies.\textsuperscript{19} Accordingly, these results have provided a foundation for the phase 3 ACNS0332 study, which includes a 2-stage (factorial) randomized design to (1) evaluate the contribution of carboptatin to the favorable results obtained in Children's Cancer Group-99701, and (2) assess the potential for enhanced survival by adding isotretinoin to an adjuvant chemotherapy backbone, which builds upon promising observations that isotretinoin can synergistically enhance the activity of platinum-based chemotherapy by inducing cytotoxicity in medulloblastoma cells. The ACNS0332 study incorporates the molecular analysis battery noted above for ACNS0331, and will also be paired with an independent correlative biology study (ACNS02B1) that will evaluate whether ex vivo resistance of tumor specimens to isotretinoin and carboptatin is associated with clinical response. This research also addresses whether pharmacological inhibitors of Wnt, Sonic hedgehog, Notch, and histone deacetylase-mediated signaling,\textsuperscript{20,21} as well as other molecular pathways implicated in medulloblastoma development, hold promise as targeted therapies for examination in future clinical studies. In addition, studies for patients with recurrent disease are focusing on various molecular targets, including growth factor receptors (eg, epidermal growth factor receptors (EGFR), ErbB2) and their downstream targets (eg, Ras, MAPK; Table 2), based on the results of the aforementioned molecular profiling studies, which noted an association between aggressive tumor behavior and both ErbB2 overexpression and Ras activation.\textsuperscript{10-16}

### High-Grade Gliomas

In contrast to the significant progress achieved in the management of medulloblastomas, the outcome of children with malignant gliomas remains poor,\textsuperscript{22-24} despite improved surgical techniques and application of newer approaches for delivering irradiation. Although the addition of chemotherapy with lomustine and vincristine to postoperative irradiation has been shown to improve survival,\textsuperscript{24} subsequent studies with more complex or intensive preirradiation and postirradiation regimens failed to further improve outcome.\textsuperscript{22,23} The 2 clinical factors associated with outcome are histology and extent of tumor resection.\textsuperscript{22,25} Not unexpectedly, patients with grade 4 lesions (ie, glioblastoma multiforme) have a worse prognosis than those with anaplastic astrocytoma or other grade 3 lesions, and those with deep-seated or highly infiltrative tumors that are not amenable to extensive resection have a worse prognosis than those with more resectable lesions. In addition, recent studies have demonstrated that a number of molecular features correlate with a worse prognosis, including overexpression and/or mutation of the tumor suppressor gene p53,\textsuperscript{26} high expression of proliferation markers such as MIB-1,\textsuperscript{27} and overexpression of methylguanine-DNA-methyltransferase, a pseudoenzyme that helps repair alkylator-induced DNA damage, thereby countering the effects of many chemotherapeutic agents.\textsuperscript{28}

On the basis of recent studies in adults that noted administering chemotherapy with temozolomide both during and after radiotherapy versus treatment with irradiation alone improved prognosis,\textsuperscript{29} a series of pediatric phase 2 studies was launched to examine this approach. The ACNS0126 study incorporated daily administration of temozolomide during radiation followed by treatment on a 5-day per 28-day schedule thereafter, coupled with independent analysis of tumor methylguanine-DNA-methyltransferase and mismatch repair status. Unfortunately, the outcome did not appear to improve in comparison to the results noted in the historical control group (Children's Cancer Group-945) treated with lomustine and vincristine. A subsequent study (ACNS0423) attempted to improve outcome by combining both lomustine and temozolomide, given a favorable rate of response and 1-year survival in a pilot study (ADVL0011) that used this combination.\textsuperscript{30} Because the significant association between both methylguanine-DNA-methyltransferase expression and p53 expression and outcome in the Children's Cancer Group-945 study was also demonstrated in the ACNS0126 cohort, these factors will be assessed in the ACNS0423 study. If their prognostic use is again demonstrated, this would provide a strong impetus for stratifying therapy based on these features in subsequent studies, if alkylator-based chemotherapy is used. Correlative studies of high-resolution genotyping and expression array analyses are also being pursued, in light of recent retrospective studies that identified genomic abnormalities and differentially expressed genes associated with tumor progression in malignant gliomas.\textsuperscript{31-33} Such exploratory analyses may identify new therapeutic targets for future studies.

In addition, the Children's Oncology Group and the Pediatric Brain Tumor Consortium have initiated phase 1 and 2 studies of pharmacological inhibitors of several molecular pathways implicated in glioma growth, such as platelet-derived growth factor receptors (PDGFR), EGFR, and related signal transduction intermediates, as well as inhibitors of angiogenic signaling, such as vascular endothelial growth factor (VEGF) and integrins, for patients with recurrent disease (Table 2).\textsuperscript{34-36} Plans are underway for a randomized evaluation of several of the most promising strategies in conjunction with standard adjuvant therapy in patients with newly diagnosed tumors.

### Brain Stem Glioma

The prognosis for children with malignant brain stem gliomas remains disappointing. The one positive accomplishment has been that neurosurgeons and neurooncologists have
become increasingly adept at distinguishing low-grade tumors, such as dorsally exophytic brain stem gliomas and focal lesions of the midbrain, medulla, and cervicomedullary junction. In contrast to the larger group of malignant brain stem gliomas, these tumors have a comparatively favorable prognosis. This has left a more homogeneous population of patients with diffuse intrinsic pontine lesions for enrollment in therapeutic studies and has facilitated a realistic appraisal of the almost uniformly dismal outcome of these biologically malignant tumors.

Because a series of studies failed to detect a benefit to the use of preradiation or postradiation chemotherapy for these tumors, both the Children’s Oncology Group and the Pediatric Brain Tumor Consortium have begun evaluating approaches for radiosensitization or combined chemoradiotherapy in an effort to potentiate the effect of radiotherapy, the single modality that has efficacy (albeit modestly so) against these tumors. The ACNS0126 study, which involved the use of temozolomide with irradiation as per the high-grade glioma study noted above, completed enrollment, and data are under analysis. A second study, ACNS0224, which opened in October 2005, involved a dose escalation of topotecan during radiotherapy, with granulocyte colony-stimulating factor support. This built upon the promising event-free survival data in the previous Children’s Oncology Group phase 1 study of this agent, and attempted to further increase the topotecan dose using granulocyte colony-stimulating factor, but unfortunately further escalation was precluded secondary to toxicity. A third study (ACNS0222) involves the use of gadolinium texaphyrin during radiotherapy, and incorporates the maximally tolerated dose determined by the recently completed A09712 phase 1 study. In all 3 studies, attention was directed toward incorporating a consistent statistical design to facilitate comparisons of the data generated with appropriate cooperative group historical control cohorts (eg, Children’s Cancer Group-9882, 9941, P9239), as well as consistent imaging and radiotherapy guidelines that would allow comparisons between studies as well as with ongoing Pediatric Brain Tumor Consortium studies.

Because previous studies have demonstrated that the vast majority of diffuse intrinsic brain stem gliomas can be diagnosed by imaging findings alone in the context of appropriate clinical symptoms, the routine use of biopsies at diagnosis to obtain tissue has fallen out of favor, which has had the unintended consequence of limiting access to biological material that might provide insights regarding relevant targets for future therapeutic studies. Addressing this challenge has been an area of intense focus in a series of joint Children’s Oncology Group/Pediatric Brain Tumor Consortium strategy—planning activities for these tumors. In pilot initiatives, investigators have begun studies of autopsy and archival surgical material, evaluating a series of hypothesis-driven targets (eg, EGFR, p53) as well as hypothesis-generating proteomic and genomic screening strategies, in parallel to studies on newly diagnosed patients with non–brain stem high-grade gliomas. The goal is to identify markers that may be sufficiently informative biologically to warrant their use in future studies as criteria for stratification at diagnosis and to pinpoint therapeutic targets that are sufficiently promising to justify application in molecularly based therapies. Several studies using molecularly targeted therapies for these tumors have already been initiated. Unfortunately, the lack of correlative specimens from treated patients has, to date, precluded defining associations, if any, between treatment response and tumor genotypic and phenotypic features, which would be useful in guiding subsequent studies.

Low-Grade Glioma

Low-grade gliomas are a diverse group that constitutes the largest subset of childhood brain tumors. Both institutional and co-operative group studies have demonstrated that extent of tumor removal is the factor with the strongest impact on outcome. Patients whose tumors have undergone gross total resection have a greater than 90% long-term survival rate. However, tumor location plays a major role in resectability; whereas most cerebral and cerebellar cortical lesions are amenable to gross total resection, midline lesions generally are not, because of the involvement of critical surrounding structures. Management of centrally located low-grade gliomas is made even more difficult because they often occur in young children, which limits the use of irradiation as a postoperative option to facilitate disease control.

In a series of recent studies, several chemotherapy regimens have been noted to have efficacy in delaying or avoiding the need for radiotherapy in children with progressive or high-risk incompletely resected tumors. The recently completed A9952 study performed a phase 3 randomized comparison of 2 active regimens, carboplatin/vincristine and 6-thioguanine–procarbazine–lomustine–vincristine. Preliminary results from this study confirmed the activity of both regimens. Many tumors, however, show disease progression within several years of diagnosis, and additional options are needed to improve treatment. Pending the final results from the A9952 study, 3 pilot studies were launched to explore options that might be included in a subsequent phase 3 protocol. ACNS0223 is examining the feasibility of building upon the carboplatin/vincristine backbone by adding temozolomide, and ADVL0515 is examining vinblastine as an alternative to vincristine in the carboplatin-containing regimen, based on the intriguing independent activity of this agent. In view of the known activity of irradiation against these tumors, ACNS0221 is evaluating the
Brain Tumors in Infants

Malignant brain tumors in children younger than 3 years have generally been managed as a distinct subset because of the extreme vulnerability of the infant brain to radiation-induced sequelae, which has necessitated age-based treatment modifications.51,52 In previous studies that have induced sequelae, which has necessitated age-based
treatment modifications.51,52 In previous studies that have
treatment modifications.51,52 In previous studies that have
been noted that 30% to 40% of children will respond favorably and not require radiotherapy, although most will develop progressive disease within 1 to 2 years of diagnosis, which ultimately proves fatal. To improve on these results with so-called “induction” chemotherapy, recent studies have examined whether adding a second phase of myeloablative “consolidation” chemotherapy (Children’s Cancer Group-99703) or focal irradiation to the tumor bed (P9934) can increase the frequency with which patients maintain long-term disease control. Preliminary data from Children’s Cancer Group-99703 suggest that survival percentages may indeed be improved and, as with the recent German Pediatric Oncology Group study of a regimen (HIT-SKK92) that added high-dose methotrexate to achieve the same goal,53 compare favorably with prior co-operative group studies using less intensive therapy. Together, these studies support the rationale of building on induction chemotherapy as a strategy to improve survival.

Recent studies have also provided major insights for the molecular classification of infant tumors, identifying a subset of “small blue cell” tumors, previously grouped with primitive neuroectodermal tumors, that have a characteristic pattern of mutations or inactivation of the INI1 gene (as assessed by sequencing or immunohistochemistry analysis or by fluorescence in situ hybridization to detect loss of this chromosome 22 locus).54,55 These tumors have been reclassified as atypical teratoid/rhabdoid tumors, and are associated with a much lower overall survival rate than noted with infant medulloblastoma and primitive neuroectodermal tumors, frequently showing rapid progression during and after induction therapy.52 Accordingly, Children’s Oncology Group infant malignant tumor studies currently stratify patients based not only on histological and clinical features but also on molecular characteristics. This represents the first effort by a pediatric co-operative group to tailor treatment based on protocol-mandated molecular categorization.

The current Children’s Oncology Group study for infants with metastatic medulloblastoma and supratentorial primitive neuroectodermal tumors (ACNS0334) incorporates this rigorous stratification approach and builds upon observations of both the Children’s Cancer Group-99703 and HIT-SKK92 studies, incorporating the backbone from Children’s Cancer Group-99703 with a randomized assessment of the efficacy and toxicity of adding methotrexate to the induction phase of therapy followed by intensive consolidation therapy as per the Children’s Cancer Group-99703 regimen. The study is designed to examine whether further intensification of induction therapy improves the frequency of achieving complete tumor regression and disease control, and whether this can be accomplished without an excessive increase in toxicity.

A second study is being developed for infants with localized medulloblastoma. This study will build upon recent data that patients with radiographically complete resections and those whose tumors have desmoplastic features have generally had a favorable response to the therapy included in the HIT-SKK92, Children’s Cancer Group-9921, and Children’s Cancer Group-99703 regimens,52,53 whereas those with residual disease whose tumors have classical histological features have had a higher incidence of disease progression. This protocol will stratify therapy based on these factors, with a goal of diminishing late sequelae of therapy in more favorable-risk patients and improving survival in those with less favorable prognostic features. Tumors will also be analyzed using the molecular battery noted earlier for medulloblastoma/primitive neuroectodermal tumors in older children (Table 1), in an effort to further refine the identification of biologically distinct tumor subsets. A third study (ACNS0333) will soon open for infants with atypical teratoid/rhabdoid tumors and will provide treatment similar to that in the methotrexate-containing arm of the ACNS0334 study in conjunction with early irradiation administered in an age-adjusted, disease state–adjusted, and response-adjusted fashion. This approach is based on the observation that most long-term survivors in previous studies have received early irradiation in addition to intensive multiagent chemotherapy.56,57 In view of the poor prognosis of atypical teratoid/rhabdoid tumors, genotyping and expression profiling of tumor samples obtained in this study will be performed in an effort to uncover prognostic indicators and potential leads for future study development.

Conclusion

Advances in surgical and adjuvant therapy have improved the prognosis for several types of childhood brain tumors,
such as medulloblastoma. The outcome for other types, such as diffuse intrinsic brain stem glioma, remains disappointing. Molecular techniques are now being introduced as a way to refine therapeutic stratification for a number of tumor subtypes, and may help identify novel targets for heretofore resistant tumors. In addition, molecularly targeted therapies are currently being examined for their activity in progressive brain tumors and are selectively being applied in the management of newly diagnosed high-risk lesions.

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