Brain Tumors

Murali Chintagumpala, MD[a,*], Amar Gajjar, MD[b]

KEYWORDS

• Medulloblastoma • Glioblastoma • Anaplastic astrocytoma
• Diffuse intrinsic pontine glioma • Ependymoma

KEY POINTS

- The past 2 decades have witnessed a revolution in the management of childhood brain tumors, with the establishment of multidisciplinary teams and national and international consortiums.
- Unprecedented cooperation within the pediatric neuro-oncology community and sophisticated rapidly evolving technology have led to advances that are likely to revolutionize treatment strategies and improve outcomes.

Brain tumors in children represent the second most common malignancy in children. The number of children, adolescents, and young adults (0–19 years) with a diagnosis of a brain tumor is approximately 4350 per year.[1] The cause for most of these tumors is unknown, but there are some predisposing conditions that give rise to certain types of brain tumors. Turcot syndrome, Li-Fraumeni syndrome, and Gorlin syndrome are examples that can give rise to high-grade glioma (HGG) and medulloblastoma.[2–4]

Management of children with brain tumors requires a multidisciplinary approach, and these children are best served at pediatric hospitals, which are equipped with the necessary resources and personnel. Pediatric neurosurgeon, oncologist, neuropathologist, neuroradiologist, radiation oncologist, endocrinologist, and physical rehabilitation services among others should be available.

These children present most commonly with symptoms related to increased intracranial pressure or one or several of the following: cranial nerve palsies, incoordination, seizures, loss of vision, and short stature.

A few of the more common brain tumors and recent advances in their management are discussed in the following sections.

[a] Texas Children's Cancer Center, Baylor College of Medicine, 6701 Fannin Street, CC1510.15, Houston, TX 77030, USA; [b] Department of Oncology, St Jude Children's Research Hospital, Room 6024, 262 Danny Thomas Place, Memphis, TN 38105, USA
* Corresponding author.
E-mail address: mxchinta@txch.org

Pediatr Clin N Am 62 (2015) 167–178
http://dx.doi.org/10.1016/j.pcl.2014.09.011 **pediatric.theclinics.com**
0031-3955/15/$ – see front matter

MEDULLOBLASTOMA

Medulloblastoma is the most common malignancy in children and represents approximately 20% of all malignant brain tumors that affect children between the ages of 0 and 14 years.[5,6] There is a bimodal distribution peak between 3 and 4 years and again between 8 and 10 years of age. It can occur in teenagers and young adults, but less frequently.

The cause of medulloblastoma is unknown. However several familial syndromes like Gorlin syndrome, Turcot syndrome, and Li-Fraumeni syndrome, which have a genetic predisposition to development of medulloblastoma, offer clues to the molecular pathologic mechanisms that can lead to growth of medulloblastoma. About 3% to 5% of children with Gorlin syndrome develop medulloblastoma. Gorlin syndrome is characterized by an inherited germline mutation of the PATCHED1 gene on chromosome 9, which encodes the sonic hedgehog (SHH) receptor PTCH1 and normally suppresses SHH signaling by inhibiting the SMO receptor.[2,7] Approximately 40% of medulloblastomas show evidence of mutations in the PTCH1, and these tumors are mostly associated with the desmoplastic variant of medulloblastoma.[2,8,9] Children with Turcot syndrome have mutations in the adenomatosis polyposis coli gene (type 2) or mutations in the DNA mismatch repair genes HPS2 and MLH1 (type 1). Patients with type 2 disease are at increased risk for developing medulloblastoma.[2,10] Approximately 10% of children with medulloblastoma have a favorable prognosis and have abnormalities in the WNT molecular pathway, which is also aberrant in Turcot syndrome. Patients with Li-Fraumeni syndrome with germline mutations in the TP53 gene can develop medulloblastoma, particularly of the SHH subtype, although gliomas are more common in this syndrome.[2,11]

Clinical Presentation

The symptoms at presentation caused by medulloblastoma are related to obstruction of cerebrospinal fluid (CSF) pathways and direct involvement of the cerebellum or the brainstem. Headaches and vomiting as a result of raised intracranial pressure, constant features later in the course of the disease, are often nonspecific in the early stages. Unsteadiness, mostly truncal, is present in about 50% to 80% of children with medulloblastoma. Esotropia in 1 or both eyes and papilledema are common. Clumsiness, dropping things frequently, and declining academic performance are other symptoms that can indicate the presence of a cerebellar lesion like medulloblastoma. Macrocephaly, unexplained lethargy, and head tilt are more common in infants.

Diagnosis

The diagnosis of medulloblastoma is initially suspected based on imaging studies, which include MRI of the brain. A typical radiographic presentation is the presence of a solid midline posterior fossa mass that seems to arise from the cerebellum and occupies the fourth ventricle. It shows variable and heterogeneous enhancement pattern. Occasionally, it may arise from the lateral aspect of either cerebellar hemisphere and often indicates a specific subtype of medulloblastoma that shows activation of the SHH pathway. The differential diagnosis of a midline posterior fossa mass includes ependymoma and pilocytic astrocytoma. The former is a solid tumor, which tends to spread toward the cerebellopontine angle via the foramen of Luschka or toward the spinal cord via the foramen of Magendie. The latter consists of solid and cystic components, with often a uniform enhancement of the solid component. In the younger child, the differential diagnosis includes atypical teratoid rhabdoid tumor, which may show involvement of the cerebellopontine angle. A complete MRI

evaluation of the full length of the spinal cord and the thecal sac is strongly recommended before surgical intervention for the primary tumor. A lumbar puncture to assess the involvement of CSF should be performed at least 2 weeks after surgical removal of the primary tumor.[12] Attempts at lumbar puncture at the time of diagnosis before alleviation of increased intracranial pressure are strongly contraindicated. In the absence of peripheral blood count abnormalities, bone marrow evaluation is not indicated. It is rare for bone metastases to be present at the time of diagnosis.

Clinical Staging

Most treatment strategies have used the modified Chang system for classification of medulloblastoma into standard-risk (average-risk) or high-risk categories.[13] A gross total resection (GTR) or near total resection of the primary (with $\leq$1.5 cm^2 of residual tumor) and the absence of metastases renders a patient as having average-risk disease. Residual tumor greater than 1.5 cm^2 or evidence of metastases indicates high-risk disease.

Management of Medulloblastoma

A multidisciplinary team is essential for optimal management of a child with medulloblastoma. Primary intervention consists of complete removal of the primary tumor and is commonly achieved at most pediatric centers in the United States. Postoperatively, one of the main complications of surgery is the appearance of posterior fossa syndrome or cerebellar mutism, which occurs approximately 72 hours after surgery. This complication is characterized by inability to speak with or without accompanying neurologic deficits. The cause of this complication is unclear. Disruption of long white matter tracts is implicated. There is no evidence that this complication can be avoided by modifying surgical technique. In 1 retrospective study of more than 400 patients,[14] approximately 25% of patients were affected by posterior fossa syndrome. Most of these patients suffer long-term severe to moderate neurocognitive deficits. There is no evidence that the course of this syndrome can be modified by medical intervention.

Radiation therapy is an important component of adjuvant therapy and was the mainstay of therapy after surgery until the early 1990s. After early reports of increased failures after radiation volumes that did not include the whole craniospinal axis, improved outcomes of approximately 70% were achieved using a standard CSI dose of 36 Gy with a posterior fossa boost to 54 Gy in patients with average-risk disease. To reduce the long-term adverse neurocognitive effects of a craniospinal radiation dose of 36 Gy, a randomized trial was initiated within the Children's Cancer Group (CCG) and Pediatric Oncology Group (POG) comparing 36 Gy to 23.4 Gy for craniospinal irradiation (CSI) with a posterior fossa boost up to 54 Gy.[15] The results of this intergroup trial showed a trend toward a better outcome with those who received 36 Gy to CSI. However in the interim, a multi-institutional study clearly showed a benefit with the use of multiagent chemotherapy (chloroethylnitrosourea [CCNU], cisplatin, and vincristine) after radiation therapy (23.4 Gy to CSI) in patients with average-risk disease.[16] The sequence of surgery followed by reduced dose of CSI and multiagent chemotherapy became the standard of care for children with medulloblastoma with average-risk disease, with an expected 5-year event-free survival (EFS) of approximately 80%. Variation of this treatment schema with decrease in duration and an increase in dose intensity of chemotherapy agents produced similar results.[17] Substitution of CCNU with cyclophosphamide in the multiagent regimen yielded similar results.[18] Tumors with anaplastic histology have a poorer outcome, especially those that have either MYC or MYCN amplification.[17] Success in improving outcomes in average-risk disease comes at a price. Significant neurocognitive effects

have been described, even with CSI dose of 23.4 Gy. Ninety percent of patients develop growth hormone deficiency, and many develop deficiencies of other hormones, requiring lifelong supplementation, which carries its own risks as a result of lack of adherence, especially in the teenage years.[18] Sensorineural deafness as a result of radiation therapy and cisplatin can also be debilitating. The current Children's Oncolgy Group (COG) trial is testing whether the use of 18 Gy to CSI can achieve the same outcome as 23.4 Gy and decrease the severity and incidence of long-term effects mentioned earlier.

The role of chemotherapy after radiation therapy in patients with medulloblastoma with high-risk disease was clearly established, with a 5-year EFS of 46% with chemotherapy.[19] Data from POG trial 9031 showed that patients with high-risk disease had a 5-year EFS of 70% with higher doses of radiation therapy and chemotherapy, including cyclophosphamide and cisplatin.[20] Similar results were obtained with more intensive chemotherapy with stem cell rescue.[17] A current trial within the COG is testing whether the use of carboplatin as a radiosensitizer and a differentiating agent (retinoic acid) can further improve the outcome in patients with high-risk disease.

Children younger than 3 years present a unique challenge. The developing brain is highly susceptible to devastating effects of radiation therapy, and therefore, clinical trials had centered on the use of chemotherapy alone and delaying the use of CSI until the patient is 3 years of age. This strategy had resulted in a poor outcome in infants, except in those infants who have nonmetastatic disease, undergo GTR, and have a particular type of histopathology, described as nodular desmoplastic or medulloblastoma with extensive nodularity. The use of higher doses of systemic methotrexate and concomitant use of intrathecal methotrexate has obviated radiation therapy in infants but still resulted in leukoencephalopathy in 19 of 23 patients tested; this could lead to long-term significant neurocognitive deficits.[21]

Recent Advances

Until recently, medulloblastoma was considered one disease and was treated uniformly with the same regimen. Northcott and colleagues,[22] along with others, showed that medulloblastoma can be categorized into 4 groups. Tumors displaying WNT pathway activation with resultant nuclear accumulation of β-catenin and monosomy 6 constitute about 10% of all children with medulloblastoma and have a favorable prognosis. Efforts are under way to significantly reduce radiation therapy or chemotherapy or both for this subtype. Approximately 30% of patients with medulloblastoma have evidence of activation of the SHH pathway as a result of mutations in the *PTCH1* or the *SMO* genes. Survival rate in this subgroup is approximately 75%. SMO inhibitors are in clinical trials, and one such trial was recently published.[23] Group 3 constitutes tumors that have a poor prognosis, with survival rate of approximately 50%; survival rate of group 4 is approximately 70%. Newer and more effective agents are needed to improve outcomes in these groups. Genomic sequencing data offer further clues to the biology of these tumors and potentially new targets. With the burgeoning data, there is increased hope for more effective and targeted therapies, which could lead to improved outcomes with lesser toxicities.

HIGH-GRADE GLIOMA AND DIFFUSE INTRINSIC PONTINE GLIOMA

Glioblastoma, anaplastic astrocytoma, and diffuse intrinsic pontine glioma (DIPG) represent the most common high-grade glial tumors in childhood, and together, up to 0.8 per 100,000 children younger than 19 years are estimated to develop HGGs each year. Therefore, along with embryonal tumors, these tumors constitute the

most common malignant neoplasms of the brain in children. DIPGs are midline tumors, and among the other HGGs, 25% occur in the deep midline structures of the cerebrum, 15% in the posterior fossa, and the rest in cerebral hemispheres.[24,25] The median age at diagnosis is 9 to 10 years for HGG and 6 to 7 years for DIPGs.

Symptoms and signs of disease manifest rapidly after a short clinical history and can be related to increased intracranial pressure characterized by headaches, seizures, or weakness on the opposite side. Children with DIPGs can present with gait imbalance and lower cranial nerve paresis, after a short prodromal phase.

HGGs are heterogeneous on computed tomography and MRI with ill-defined margins, usually with marked surrounding edema, hemorrhage, necrosis, mass effect, and irregular enhancement. These tumors show restricted diffusion on apparent diffusion coefficient maps on MRI and a marked increase in choline levels with a reduction in *N*-acetyl aspartate on magnetic resonance spectroscopy. On perfusion imaging, these tumors tend to have high relative cerebral blood volume values. MRI findings in DIPGs are similar and are characterized by a diffuse expansion of the pons which is isointense or hypointense on T1 and bright on T2 sequences.

HGGs show several histologic features of malignancy, including hypercellularity, cytologic and nuclear atypia, mitoses, necrosis with or without pseudopalisading, and vascular proliferation with endothelial hyperplasia. The most common malignant glial neoplasms are anaplastic astrocytoma and glioblastoma multiforme, which may alternatively be termed grade III and grade IV astrocytomas, respectively.

HGGs often show a histologically heterogeneous nature, and areas of low-grade histology may be seen particularly in small biopsies taken from the more superficial areas of tumor. Therefore, more generous sampling is recommended to avoid confusion about the true nature of the HGG. The pathologic features may vary in DIPGs. There could be regions with low-grade, diffuse, fibrillary-type, World Health Organization (WHO) grade II histopathology, or, more often, high-grade anaplastic astrocytoma (WHO grade III) or glioblastoma multiforme (WHO grade IV).

Treatment

Surgery

Removal of more than 90% of the tumor confers a favorable prognosis in HGG.[25] The infiltrative nature of the tumor does not render itself to complete resection. Local progression therefore is common, thus resulting in a poor prognosis.

Radiation therapy and chemotherapy

Postoperative radiation therapy is the mainstay of therapy in children with HGG. Although rarely curative, the addition of radiation alone had shown improved survival in children, with higher rates of 1-year to 3-year disease control. Postoperative therapy incorporates wide local irradiation. The radiation field typically includes enhancing tumor on T1 and the perilesional infiltration estimated by findings on T2 or fluid-attenuated inversion recovery sequences. Typical dose is 54 to 60 Gy in pediatrics. The role of chemotherapy in addition to postoperative radiotherapy is still unclear. Initial encouraging results with a chemotherapy regimen consisting of prednisone, vincristine, and CCNU (pCV regimen) showed that progression-free survival (PFS) for children receiving postradiation chemotherapy was significantly higher (46%) than for those receiving radiation therapy alone (16%; $P = .026$).[26] A subsequent trial conducted by CCG (CCG-945), which is one of the largest pediatric trials in children with HGG, randomized patients to receive adjuvant chemotherapy with an 8-in-1 regimen or PCV (P, procarbazine). No difference was observed between the 2 chemotherapy arms, and 5-year PFS rates were 33% and 36% for 8-in-1 chemotherapy and

PCV, respectively.[25] Thus, there seemed to be little benefit from addition of chemotherapy, when compared with surgery and radiation therapy alone. A recent COG trial, ACNS0126, combined radiation therapy with temozolomide, 90 mg/m^2/d, daily for 42 days, followed by 10 cycles of adjuvant temozolomide, 200 mg/m^2/d $\times$ 5 days given every 28 days.[27] EFS for 99 eligible patients with HGG on ACNS0126 was compared with a similar cohort of 122 patients from CCG-945, which was open to accrual between 1985 and 1992. Outcome for ACNS0126 did not significantly differ from historical controls, with 1-year EFS of 39% $\pm$ 5% for ACNS0126 compared with 42% $\pm$ 4.5% for CCG-945 (logrank P = .14). Patients with low/absent methyl guanine methyl transferase expression had longer EFS and overall survival, and therefore, temozolomide may be useful as part of a chemotherapy regimen for future studies in this subgroup of patients. Another approach to circumventing temozolomide resistance is through inhibition of PARP (poly-ADP ribose polymerase), a critical nuclear enzyme that activates proteins in the base excision repair and other DNA repair pathways. Inhibition of this enzymatic activity with a PARP inhibitor such as ABT-888 may overcome temozolomide resistance. Trials with ABT-888 and temozolomide are in progress. The use of concurrent radiation and temozolomide followed by temozolomide and lomustine for pediatric HGGs was evaluated in a COG trial (ACNS0423) and the results are yet to be published. A COG trial with involved-field radiation with concurrent vorinostat or temozolomide or bevacizumab followed by maintenance with bevacizumab and temozolomide was recently completed.

In the management of children with DIPG, radiation therapy is the mainstay of treatment. Improvement in symptoms, signs, and neuroimaging occurs in most children, although the duration of benefit is measured in months, with few long-term survivors.[28,29] Variations in the delivery and total dose of radiation therapy were attempted. Hyperfractionated delivery consisting of twice-daily irradiation with fractions of 1.0 to 1.25 Gy to total doses ranging from 64.8 to 78.0 Gy showed no significant improvement.[29–32] A randomized trial comparing hyperfractionated radiation at dose level of 70.2 Gy with conventional fractionation (1.8 Gy once daily to 55.8 Gy) showed no difference, leading North American centers to consider conventional fractionation as the standard for current management and trials.[33]

Attempts at radiosensitization using *cis*-platinum concurrently with radiation seemed to show similar or marginally inferior outcome for children with brainstem tumors when compared with radiation alone.[34] Various agents have been used with radiation therapy to improve outcome in these patients, with little benefit.

The Pediatric Brain Tumor Consortium conducted a phase 1 trial with radiation therapy and capecitabine.[35,36] It was well tolerated, and a phase 2 trial is in progress. Radiation therapy is a potent inducer of thymidine phosphorylase (TP), which converts capecitabine to 5-fluorouracil within the tumor. Capecitabine antitumor activity is correlated with intratumoral TP; therefore, this combination may be more effective than radiotherapy alone for brainstem gliomas.

Advances in the management of DIPG have been hindered by the lack of tissue specimens to gain insights into the biology of these tumors. Recent data from autopsy specimens have provided much information, as discussed later. Also, current protocols, which require a biopsy of these tumors before initiation of therapy, are likely to shed more light on the pathways leading to tumor formation.

Recent advances in high-grade glioma and diffuse intrinsic pontine glioma

Recently, rapid advances in molecular biology have generated detailed catalogs of genomic and epigenomic alterations in HGG and DIPG in children. Using many samples from children with HGG and DIPG, sequencing studies showed recurrent

heterozygous mutations in histone H3F3A, with amino acid substitutions at positions K27 or G34. K27 was also found to be mutated in the H3.1 histone genes *HIST1H3B* and *HIST1H3C*.[37,38] These mutations directly or indirectly target important sites on the histone tail for posttranslational modifications. H3 mutations occur exclusively in approximately 38% of childhood, and young adult patients with HGG and are mutually exclusive with respect to mutations in IDH1.[37,39] Mutations in H3F3A, which result in amino acid changes at K27, occur in 70% to 80% of midline glioblastoma multiforme and DIPG in younger children.[38,40,41] Mutations in H3F3A that result in amino acid changes at G34 occur in adolescents at around the age of 20 years who have disease exclusively located in hemispheric regions. Mutations at K27 seem to confer a dismal prognosis, whereas G34 mutations seem to be associated with slightly prolonged overall survival.[40,41] Novel activating mutations in ACVR1 are identified in approximately 20% of children with DIPG. Taken together, these data raise the possibility of developing targeted therapies against these known mutations and thereby improve outcomes in these children, who collectively have a dismal prognosis with the current therapies.

EPENDYMOMA

Ependymomas represent approximately 10% of all primary tumors of the central nervous system in children. These tumors arise from the ependymal lining of the ventricular system or the central canal of the spinal cord. Ninety percent of the tumors are intracranial, and up to two-thirds of these occur in the posterior fossa. There are 2 peaks in incidence: one in the first 7 years of life and the second in the third to fifth decades of life.[42] The ratio of male to female is between 1.3 and 2.0.

Within the posterior fossa, ependymomas represent the fourth most common posterior fossa tumor in children, after medulloblastoma, cerebellar astrocytoma, and brainstem glioma. They usually grow out of the fourth ventricle via the foramina of Luschka and Magendie toward the cerebellopontine angle and through the foramen magnum into the upper cervical canal around the spinal cord. On MRI, these tumors are heterogeneous, containing cysts, calcification, and occasional hemorrhage, as well as irregular, heterogeneous enhancement with gadolinium.

Ependymomas vary from well-differentiated tumors with no anaplasia, rare or absent mitoses, and mild pleomorphism to highly cellular lesions with brisk mitotic activity, anaplasia, microvascular proliferation, and pseudopalisading necrosis. The former are low-grade tumors (WHO grade II) and the latter are high-grade, anaplastic tumors (WHO grade III). Recent data[43,44] suggest a significant correlation between anaplastic histology and a higher rate of disease recurrence. Spinal subarachnoid dissemination has been estimated to be 7% to 12%, most commonly occurring in high-grade and posterior fossa tumors.[42,45]

Treatment

Surgery

The single most important prognostic factor in the management of ependymoma is the extent of tumor resection. The survival rate is higher after a GTR (66%–75%) versus a less complete resection (0%–11%). However, in most series, only approximately 60% to 70% of patients undergo a GTR. GTRs are generally more difficult for posterior fossa ependymomas than for supratentorial ependymomas, because of the propensity for infratentorial lesions to infiltrate the brainstem and to surround cranial nerves and vessels lateral and ventral to the brainstem. Infants are particularly likely to have large infratentorial ependymomas, and this is one of the reasons why

they have a less favorable prognosis.[46–48] Aggressive surgical procedures to confer a good prognosis can result in multiple lower cranial nerve palsies, which often necessitate a tracheostomy and gastric feeding device. Recent treatment protocols have allowed for second-look surgery to be performed after initial chemotherapy to make complete resections safe.

Radiation therapy

Local postoperative radiation therapy has increased the overall survival rates of patients with ependymoma from approximately 60% to 85%.[49] There are data to suggest that radiation therapy may not be necessary in patients with well-differentiated supratentorial ependymomas and intramedullary spinal cord or cauda equina.[50,51]

In a large prospective study of 153 children with localized ependymomas, GTR and conformal, high-dose, postoperative radiation (59.4 Gy with a 1-cm margin around the target volume) resulted in a 7-year local control, EFS, and overall survival rates of 87.3%, 69.1%, and 81.0%, respectively.[49] However, local failure continues to be the greatest obstacle to improving clinical outcome in children with ependymoma, with local failures occurring in 59% to 97% of recurrent cases, and isolated local failure accounting for 39% of failures in the large series reported by Merchant and colleagues.

The recently closed COG trial ACNS 0121 used a 1-cm margin, which most consider the standard of care. However, the most recent COG prospective study incorporates further reduction in treatment volume, with only a 0.5-cm margin around the target volume to 54 Gy and no clinical target volume expansion for the final boost to 59.4 Gy.

Although chemotherapy is considered to be active in this disease, with good response rates to various chemotherapeutic agents, their contribution to overall survival is still not proved. The recently completed COG ACNS0121 trial will provide data as to whether 2 cycles of multiagent chemotherapy in patients with subtotal resections make their tumors more amenable to a GTR before the initiation of conformal radiation therapy, and the ongoing ACNS0831 study will examine the contribution of postradiation chemotherapy to improve outcome compared with patients who undergo radiation therapy alone in patients who have a GTR. The chemotherapy regimen is based on a recently reported study that showed similar EFS in patients with subtotal resection who received chemotherapy in addition to radiation therapy compared with those with complete resection and who received radiation therapy alone.

Future treatment strategies in ependymoma will be based on the advances made in the biology of these tumors. Recent advances, as discussed in the following section, clearly indicate that all intracranial ependymomas are not the same. Furthermore, these advances have given us potential target, which can lead to innovative therapies, which are likely to improve outcomes with less morbidity.

Recent advances

Location of the tumor and molecular data define 4 subtypes of ependymoma-supratentorial, posterior fossa type A (PFA), posterior fossa type B (PFB) and spinal cord ependymoma. PFA and PFB also differ in age of onset and prognosis.[52] The PFA subtype is found predominantly in infants and is associated with a poor prognosis, despite maximally aggressive therapy. The PFB subtype occurs in older children and adults and carries a good prognosis.

Among supratentorial tumors, Parker and colleagues[53] found frequent cases in which translocation of a region of chromosome 11 caused the fusion of 2 genes, RELA and C11orf95. Wild-type RELA is located in the cytoplasm, but the C11orf95-RELA

hybrid protein spontaneously translocates to the nucleus, where it activates the expression of target genes. The sequencing of posterior fossa tumors did not show any recurrently mutated gene or translocation. It has been suspected that defective epigenetic modifications might also be oncogenic. These modifications include methylation or acetylation of DNA or DNA-associated chromatin proteins. Mack and colleagues[54] did find increased DNA methylation of specific genes, as well as silencing of their expression, in PFA, but not PFB, ependymomas. PFB differs from PFA in that it is associated with gains and losses of entire chromosomes or large chromosomal fragments. Therefore, it will be challenging to test whether chromosomal gains and losses or epigenetic modifications without gene mutations can drive cancer development. The clinical implications of these alternative oncogenic routes can be far reaching, because most research has focused on drugs that target gene mutations.

SUMMARY

The past 2 decades have witnessed a revolution in the management of childhood brain tumors, with the establishment of multidisciplinary teams and national and international consortiums. Unprecedented cooperation within the pediatric neuro-oncology community and sophisticated rapidly evolving technology have led to advances that are likely to revolutionize treatment strategies and improve outcomes.

REFERENCES

1. Central Brain Tumor Registry of the United States (CBTRUS). Fact sheet. Stromberg Allen; 2013. Available at: www.cbtrus.org.
2. Taylor MD, Mainprize TG, Rutka JT. Molecular insight into medulloblastoma and central nervous system primitive neuroectodermal tumor biology from hereditary syndromes: a review. Neurosurgery 2000;47:888–901.
3. Malkin D, Li FP, Strong LC, et al. Germ line p53 mutations in a familial syndrome of breast cancer, sarcomas, and other neoplasms. Science 1990;250:1233–8.
4. Liaw D, Marsh DJ, Li J, et al. Germline mutations of the PTEN gene in Cowden disease, an inherited breast and thyroid cancer syndrome. Nat Genet 1997;16:64–7.
5. Louis DN, Ohgaki H, Wiestler OD, et al, editors. WHO classification of tumors of the central nervous system. Lyon (France): IARC; 2007.
6. Ostrom QT, Gittleman H, Liao P et al. Central Brain Tumor Registry of the United States. Statistical report, primary brain and central nervous system tumors diagnosed in the United States, 2007–2011. Central Brain Tumor Registry of the United States. Neuro-oncology 2014; 16(Suppl 4).
7. Amlash SF, Riffaud L, Brassier G, et al. Nevoid basal cell carcinoma syndrome: relation with desmoplastic medulloblastoma in infancy. Cancer 2003;98:618–24.
8. Thompson MC, Fuller C, Hogg TL, et al. Genomics identifies medulloblastoma subgroups that are enriched for specific genetic alterations. J Clin Oncol 2006;24:1924–31.
9. Eberhart CG, Kepner JL, Goldthwaite PT, et al. Histopathologic grading of medulloblastomas: a Pediatric Oncology Group study. Cancer 2002;94:552–60.
10. Clifford SB, Lusher MR, Lindsey JC, et al. Wnt/wingless pathway activation and chromosome 6 loss characterize a distinct molecular sub-group of medulloblastomas associated with a favorable prognosis. Cell Cycle 2006;5:2666–70.
11. Srivastava S, Zou ZQ, Pirollo K, et al. Germ-line transmission of a mutated p53 gene in a cancer-prone family with Li-Fraumeni syndrome. Nature 1990;348:747–9.

12. Gajjar A, Fouladi M, Walter AW, et al. Comparison of lumbar and shunt cerebrospinal fluid specimens for cytologic detection of leptomeningeal disease in pediatric patients with brain tumors. J Clin Oncol 1999;17(6):1825–8.
13. Bartlett F, Kortmann R, Saran F. Medulloblastoma. Clin Oncol (R Coll Radiol) 2013;25(1):36–45.
14. Robertson PL, Muraszko KM, Holmes EJ, et al. Incidence and severity of postoperative cerebellar mutism syndrome in children with medulloblastoma: a prospective study by the Children's Oncology Group. J Neurosurg 2006;105(6 Suppl):444–51.
15. Thomas PR, Deutsch M, Kepner JL, et al. Low-stage medulloblastoma: final analysis of trial comparing standard-dose with reduced-dose neuraxis irradiation. J Clin Oncol 2000;18:3004–11.
16. Packer RJ, Goldwein J, Nicholson HS, et al. Treatment of children with medulloblastomas with reduced-dose craniospinal radiation therapy and adjuvant chemotherapy: a Children's Cancer Group Study. J Clin Oncol 1999;17:2127–36.
17. Gajjar A, Chintagumpala M, Ashley D, et al. Risk-adapted craniospinal radiotherapy followed by high-dose chemotherapy and stem-cell rescue in children with newly diagnosed medulloblastoma (St Jude Medulloblastoma-96): long-term results from a prospective, multicentre trial. Lancet Oncol 2006;7(10):813–20.
18. Packer RJ, Gajjar A, Vezina G, et al. Phase III study of craniospinal radiation therapy followed by adjuvant chemotherapy for newly diagnosed average-risk medulloblastoma. J Clin Oncol 2006;24(25):4202–8.
19. Zeltzer PM, Boyett JM, Finlay JL, et al. Metastasis stage, adjuvant treatment, and residual tumor are prognostic factors for medulloblastoma in children: conclusions from the Children's Cancer group 921 randomized phase III study. J Clin Oncol 1999;17:8322–45.
20. Tarbell NJ, Friedman H, Polkinghorn WR, et al. High-risk medulloblastoma: a Pediatric Oncology Group randomized trial of chemotherapy before or after radiation therapy (POG 9031). J Clin Oncol 2013;31(23):2936–41.
21. Rutkowski S, Bode U, Deinlein F, et al. Treatment of early childhood medulloblastoma by postoperative chemotherapy alone. N Engl J Med 2005;352:978–86.
22. Northcott PA, Korshunov A, Witt H, et al. Medulloblastoma comprises four distinct molecular variants. J Clin Oncol 2011;29(11):1408–14.
23. Gajjar A, Stewart CF, Ellison DW, et al. Phase I study of vismodegib in children with recurrent or refractory medulloblastoma: a pediatric brain tumor consortium study. Clin Cancer Res 2013;19(22):6305–12.
24. Heideman RL, Kuttesch J Jr, Gajjar AJ, et al. Supratentorial malignant gliomas in childhood: a single institution perspective. Cancer 1997;80:497–504.
25. Finlay JL, Boyett JM, Yates AJ, et al. Randomized phase III trial in childhood high-grade astrocytoma comparing vincristine, lomustine, and prednisone with the eight-drugs-in-1-day regimen. Children's Cancer Group. J Clin Oncol 1995;13:112–23.
26. Sposto R, Ertel IJ, Jenkin RD, et al. The effectiveness of chemotherapy for treatment of high grade astrocytoma in children: results of a randomized trial. A report from the Children's Cancer Study Group. J Neurooncol 1989;7:165–77.
27. Cohen KJ, Pollack IF, Zhou T. Temozolomide in the treatment of high-grade gliomas in children: a report from the Children's Oncology Group. Neuro Oncol 2011;13(3):317–23.
28. Freeman CR, Farmer JP. Pediatric brain stem gliomas: a review. Int J Radiat Oncol Biol Phys 1998;40:265–71.

29. Packer RJ, Boyett JM, Zimmerman RA, et al. Hyperfractionated radiation therapy (72 Gy) for children with brain stem gliomas. A Children's Cancer Group Phase I/II Trial. Cancer 1993;72:1414–21.
30. Freeman CR, Krischer JP, Sanford RA, et al. Final results of a study of escalating doses of hyperfractionated radiotherapy in brain stem tumors in children: a Pediatric Oncology Group study. Int J Radiat Oncol Biol Phys 1993; 27:197–206.
31. Shrieve DC, Wara WM, Edwards MS, et al. Hyperfractionated radiation therapy for gliomas of the brainstem in children and in adults. Int J Radiat Oncol Biol Phys 1992;24:599–610.
32. Packer RJ, Boyett JM, Zimmerman RA, et al. Outcome of children with brain stem gliomas after treatment with 7800 cGy of hyperfractionated radiotherapy. A Children's Cancer Group phase I/II trial. Cancer 1994;74:1827–34.
33. Mandell LR, Kadota R, Freeman C, et al. There is no role for hyperfractionated radiotherapy in the management of children with newly diagnosed diffuse intrinsic brainstem tumors: results of a Pediatric Oncology Group phase III trial comparing conventional vs. hyperfractionated radiotherapy. Int J Radiat Oncol Biol Phys 1999;43:959–64.
34. Freeman CR, Kepner J, Kun LE, et al. A detrimental effect of a combined chemotherapy-radiotherapy approach in children with diffuse intrinsic brain stem gliomas? Int J Radiat Oncol Biol Phys 2000;47:561–4.
35. Kilburn LB, Kocak M, Schaedeli Stark F, et al. Phase I trial of capecitabine rapidly disintegrating tablets and concomitant radiation therapy in children with newly diagnosed brainstem gliomas and high-grade gliomas. Neuro Oncol 2013; 15(6):759–66.
36. Sawada N, Ishikawa T, Sekiguchi F, et al. X-ray irradiation induces thymidine phosphorylase and enhances the efficacy of capecitabine (Xeloda) in human cancer xenografts. Clin Cancer Res 1999;5:2948–53.
37. Schwartzentruber J, Korshunov A, Liu XY, et al. Driver mutations in histone H3.3 and chromatin remodelling genes in paediatric glioblastoma. Nature 2012;482:226–31.
38. Wu G, Broniscer A, McEachron TA, et al. Somatic histone H3 alterations in pediatric diffuse intrinsic pontine gliomas and non-brainstem glioblastomas. Nat Genet 2012;44:251–3.
39. Downing J, Wilson RK, Zhang J, et al. The Pediatric Cancer Genome Project. Nat Genet 2012;44:619–22.
40. Khuong-Quang DA, Buczkowicz P, Rakopoulos P, et al. K27M mutation in histone H3.3 defines clinically and biologically distinct subgroups of pediatric diffuse intrinsic pontine gliomas. Acta Neuropathol 2012;124:439–47.
41. Sturm D, Witt H, Hovestadt V, et al. Hotspot mutations in *H3F3A* and *IDH1* define distinct epigenetic and biological subgroups of glioblastoma. Cancer Cell 2012; 22:425–37.
42. Kun LE, Kovnar EH, Sanford RA. Ependymomas in children. Pediatr Neurosci 1988;14:57–63.
43. Tihan T, Zhou T, Holmes E, et al. The prognostic value of histological grading of posterior fossa ependymomas in children: a Children's Oncology Group study and a review of prognostic factors. Mod Pathol 2008;21:165–77.
44. Merchant TE, Jenkins JJ, Burger PC, et al. Influence of tumor grade on time to progression after irradiation for localized ependymoma in children. Int J Radiat Oncol Biol Phys 2002;53:52–7.
45. Vanuytsel L, Brada M. The role of prophylactic spinal irradiation in localized intracranial ependymoma. Int J Radiat Oncol Biol Phys 1991;21:825–30.

46. Duffner PK, Horowitz ME, Krischer JP, et al. The treatment of malignant brain tumors in infants and very young children: an update of the Pediatric Oncology Group experience. Neuro Oncol 1999;1:152–61.
47. Nagib MG, O'Fallon MT. Posterior fossa lateral ependymoma in childhood. Pediatr Neurosurg 1996;24:299–305.
48. Sanford RA, Kun LE, Heideman RL, et al. Cerebellar pontine angle ependymoma in infants. Pediatr Neurosurg 1997;27:84–91.
49. Merchant TE, Li C, Xiong X, et al. Conformal radiotherapy after surgery for paediatric ependymoma: a prospective study. Lancet Oncol 2009;10:258–66.
50. Hukin J, Epstein F, Lefton D, et al. Treatment of intracranial ependymoma by surgery alone. Pediatr Neurosurg 1998;29:40–5.
51. Wallner KE, Wara WM, Sheline GE, et al. Intracranial ependymomas: results of treatment with partial or whole brain irradiation without spinal irradiation. Int J Radiat Oncol Biol Phys 1986;12:1937–41.
52. Witt H, Mack SC, Ryzhova M, et al. Delineation of two clinically and molecularly distinct subgroups of posterior fossa ependymoma. Cancer Cell 2011;20(2):143–57.
53. Parker M, Mohankumar KM, Punchihewa C, et al. C11orf95-RELA fusions drive oncogenic NF-κB signalling in ependymoma. Nature 2014;506(7489):451–5.
54. Mack SC, Witt H, Piro RM, et al. Epigenomic alterations define lethal CIMP-positive ependymomas of infancy. Nature 2014;506(7489):445–50.