Pediatric Brain Tumors: Current Treatment Strategies and Future Therapeutic Approaches

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Summary: Pediatric CNS tumors are the most common solid tumors of childhood and the second most common cancer after hematological malignancies accounting for approximate 20 to 25% of all primary pediatric tumors. With over 3,000 new cases per year in the United States, childhood CNS tumors are the leading cause of death related to cancer in this population. The prognosis for these patients has improved over the last few decades, but current therapies continue to carry a high risk of significant side effects, especially for the very young. Currently a combination of surgery, radiation, and chemotherapy is often used in children greater than 3 years of age. This article will outline current and future therapeutic strategies for the most common pediatric CNS tumors, including primitive neuroectodermal tumors such as medulloblastoma, as well as astrocytomas and ependymomas. **Key Words:** Pediatric brain tumor, therapy, primitive neuroectodermal tumors, medulloblastoma, astrocytoma, ependymoma.

PRIMITIVE NEUROECTODERMAL TUMORS

Primitive neuroectodermal tumors (PNETs) consist of poorly undifferentiated, small, monomorphic round cells. Based on their location, these tumors are divided into infratentorial and supratentorial primitive neuroectodermal tumors (sPNET). The term medulloblastoma is generally used for PNETs located infratentorially in the posterior fossa. Growing evidence suggests that these tumors are a heterogenous group of undifferentiated tumors, which might have an impact on specific treatment options. Specifically, different molecular genetic aberrations in the tumor cells of medulloblastomas and sPNETs were identified, suggesting that different signaling pathways are involved in the tumorigenesis of these tumors.[1–4]

Medulloblastoma

Introduction. Medulloblastomas account for 20% of all childhood CNS tumors and 40% of all cerebellar tumors. Peak occurrence is at 4 years of age. Approximately 10 to 15% are diagnosed in infancy and require specific treatment considerations, which will be discussed in detail in this article. Treatment protocols are based on risk stratification, which takes into account age at presentation, residual disease, as well as evidence of disseminated disease. Patients greater than 3 years of age with minimal residual disease are classified as an average risk group. Children younger than 3 years, with subtotal resection and/or evidence of disseminated disease are grouped into high-risk patients.

Current treatment strategies

Surgery. Surgical resection remains the mainstay of therapy with the goal of gross total resection (GTR). Virtually all patients who present with a posterior fossa mass will undergo an open craniotomy. Studies have shown that patients with less then 1.5 cm^2 residual disease had improved survival.[5–7] Some patients might require a ventricular shunt or third ventriculostomy prior to resection of the tumor. The majority of patients will have resolution of the hydrocephalus after tumor resection, but approximately 40% will require permanent shunt placement. Prognostic factors for permanent shunting are young age, significant pre-surgical hydrocephalus, and large tumors.[8] One postsurgical complication characteristically developing after posterior fossa tumor resection is the cerebellar mutism syndrome (CMS) also referred to as the posterior fossa syndrome. This entity typically starts within 1 to 2 days after surgery, persists for weeks

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to months, and consists of paucity of speech leading to mutism, hypotonia, ataxia, and emotional instability. In addition, brainstem dysfunction can be seen, including dysphagia, facial weakness, and abducens paralysis. In one large study of 450 children, CMS developed after surgery in 107 (24%). Only brainstem involvement was predictive for the development of CMS.[9] Another series analyzed 253 children in which CMS developed in 20. All of these cases had brainstem involvement.[10] Evidence of hydrocephalus also appears to exacerbate the development of CMS.[11] Individual case studies report on successful use of dopamine agonists, such as bromocriptine for the treatment of CMS,[12,13] but unfortunately children are often left with dysarthric speech. Therefore, careful resection is warranted, especially in children with brainstem involvement.

Radiation

Medulloblastomas are very radiosensitive tumors and adjuvant therapy with radiation has been the standard of care in children >3 years of age. The reported, long-term side effects of radiation therapy, such as hearing loss,[14,15] cognitive decline,[16] endocrine abnormalities,[17] vascular complications,[18] as well as secondary malignancies,[19] have inspired many investigators over the years to try to reduce the amount of radiation, as well as the radiation field albeit with limited success. The Pediatric Oncology Group (POG) and Children's Cancer Group (CCG), now collectively known as the Children's Oncology Group (COG), compared in a prospective trial (POG 631/COG 923) reduced neuroaxis radiation of 23.6 Gy to the standard regimen of 36 Gy with equal posterior fossa radiation (54 Gy) for children with average risk medulloblastoma. The interim analysis indicated an increased risk of early relapse with reduced radiation.[20] The long-term follow-up analysis of these children confirmed these early results, but also showed that over time these differences are less pronounced. The 8-year analysis of this trial revealed no statistical difference between the two treatment groups.[21] Since then, many studies have focused on the introduction of chemotherapy to reduce radiation exposure, but maintain adequate survival, which will be discussed below. The introduction of conformal radiation enabled radiation oncologists to reduce the radiation field. A multi-institutional prospective trial using 23.4 Gy craniospinal irradiation followed by conformal posterior fossa (36 Gy) and primary site irradiation (55.8 Gy), and dose-intensive chemotherapy for average risk medulloblastoma achieved similar disease control than irradiation of the complete posterior fossa.[22] Other investigators used a boost dose to the tumor bed, instead of irradiating the entire posterior fossa using conformal radiation therapy with 5-year overall survival (OS) rates of 84%.[23] Proton beam therapy is another alternative to conventional radiation therapy. The benefit of using proton beams is the higher proportion of tumor versus normal tissue distribution. An ongoing phase II trial at the Massachusetts General Hospital in Boston is assessing the efficacy and long-term cognitive outcome in patients who receive proton beam therapy to the posterior fossa and craniospinal axis. Radiosurgery can successfully be used for local tumor control in patients with recurrent or residual disease.[24–26] However, stereotactic radiation as primary treatment modality is limited given the propensity of medulloblastomas for dissemination and treatment failure can occur due to subclinical craniospinal metastasis.

The current standard for average risk medulloblastoma in North America includes postoperative craniospinal irradiation of 23.4 Gy, plus a boost to the posterior fossa of 54 Gy followed by 12 months of chemotherapy. This regimen has resulted in a 5-year OS of 80% or better.[27] In high-risk disease, 36 Gy craniospinal irradiation, plus a boost at the posterior fossa of 54 Gy, followed by chemotherapy is standard. Ongoing trials are investigating the benefit of chemotherapy during irradiation.

Chemotherapy

Lowering the radiation dose without adding chemotherapy has led to worse outcomes in children with medulloblastoma. Many studies have investigated the role of chemotherapy in addition to radiation therapy with the goal to reduce the amount of radiation exposure. A range of different chemotherapeutic agents has been used and is now standard of care in the management of children with medulloblastoma in all risk groups. Alkylators and platinum compounds, such as lomustine, cyclophosphamide, and cisplatin remain key therapeutic agents. Vincristine is often administered weekly during irradiation and as adjuvant chemotherapy. Children with average risk disease, who were treated with craniospinal irradiation of 23.4 Gy and 55.8 Gy to the posterior fossa, as well as adjuvant chemotherapy (lomustine, vincristine, and cisplatin) showed a progression-free survival (PFS) of 86% (± 4%) at 3 years and 79% (± 7%) at 5 years.[28] The European Hirntumor (HIT) 91 trial compared outcome in patients with average risk medulloblastoma receiving either neoadjuvant chemotherapy (prior to radiation therapy) or postradiation chemotherapy. In this study, patients with residual tumor and M1 disease were included, which differs from most United States' studies. The 5-year PFS in the postradiation chemotherapy arm was reported at 78% (± 6%), and in the neoadjuvant chemotherapy arm as 65% (± 5%).[29] The PNET III trial conducted in the United Kingdom by the International Society of Pediatric Oncology compared PFS in average risk medulloblastoma patients (including patients with M1 disease) treated with either radiation therapy alone (35 Gy of craniospinal irradiation with a total dose of 55 Gy to the posterior fossa) or a combination of chemotherapy (vincristine, carboplatin, cy-

clophosphamide, and etoposide) and radiation therapy. The 5-year PFS was 74% in the group receiving chemotherapy and radiation therapy compared with 60% for the radiation group.[30] Collectively, these studies confirm the benefit of adjuvant chemotherapy for the treatment of average risk medulloblastoma. Currently, the regimen reported by Packer et al.,[28] as previously described remains the standard of therapy for low-risk medulloblastoma patients in North America.

For high-risk medulloblastoma patients, the priority remains to improve survival. Average event-free survival (EFS) at 5 years for high-risk medulloblastoma ranges from 34 to 40% across studies.[31] Multiple studies have used different chemotherapy protocols, including neoadjuvant chemotherapy in combination with surgery and radiation to improve survival with moderate success.[7,29] The use of prolonged neoadjuvant chemotherapy resulted in inferior outcomes compared with those obtained with shorter times between surgery and radiation therapy.[29,31] Other avenues like myeloablative chemotherapy with stem cell rescue, as well as intrathecal and intravenous methotrexate have been used for the treatment of high-risk medulloblastomas with various success.[32,33] The best outcome for high-risk medulloblastoma patients to date was achieved by craniospinal irradiation (36 Gy M0-1; 39.6 Gy M2-3) with a boost to the primary tumor site after maximal surgical resection followed by dose-intensive cyclophosphamide, vincristine, and cisplatin chemotherapy with autologous peripheral blood stem cell rescue. The 5-year EFS was 70%.[34] The COG (COG 99701) treated 57 patients with metastatic medulloblastoma with vincristine and carboplatin while receiving radiation therapy (36 Gy for craniospinal irradiation), followed by monthly treatment with cyclophosphamide and vincristine. The-4 year OS and EFS were reported at 81% (± 5%) and 66% (± 6%), respectively. Patients with anaplasia had worse outcomes (4-year OS 65% ± 11%) compared with patients with no anaplasia (4-year OS 89% ± 5%).[35] This indicates that chemotherapy is also pivotal for the treatment of high-risk medulloblastoma patients, but ongoing studies are investigating the best regimen for these patients.

Medulloblastoma in the very young child

Medulloblastoma is the most common brain tumor in childhood and one third of the cases are present in the first years of life. Management of these very young patients remains challenging since the immature brain is particularly susceptible to the toxicity of current treatment options. There is belief that medulloblastomas in the very young child have a more aggressive behavior and a higher incidence of metastasis at the time of diagnosis, although the data is limited. Evans et al.[36] reported that 34% of children under the age of 4 years presented with disseminated disease compared with only 14% of children aged 4 years or older. Similar results were reported separately with 62% of children less than 5 years of age demonstrating metastatic disease versus 38% in children older than 5 years of age.[37] The impact of age on prognosis is difficult to assess because younger patients normally receive different treatment modalities than older children. In an attempt to delay or obviate radiation therapy, multiple studies have been performed using different chemotherapy regimens.

In 1985 van Eys et al.[38] published their encouraging results using postoperative neoadjuvant chemotherapy. Two of 6 children younger than 4 years of age with medulloblastoma treated with a postoperative course of mechlorethamine, vincristine, procarbazine, and prednisone remained in complete remission. In the mid-1980s, the POG conducted a trial (referred to as Baby-POG I) enrolling 102 children less than 3 years of age with brain tumors in which prolonged postoperative chemotherapy was given with an attempt to delay radiation therapy. The 5-year PFS of 62 children with medulloblastoma less than 3 years of age was reported at 31.8% (± 8.3%) and the 5-year OS at 39.7 % (± 6.9%) using a combination of cyclophosphamide, vincristine, cis-platinum, and etoposide. Radiation was delayed until 3 years of age. The main predictor for survival was extent of surgical resection. Tweny children undergoing GTR had a 5-year OS of 60% compared with 33 children who had subtotal resection and who had a 5-year OS of 32%.[39] Other studies investigated a similar approach. The CCG used the "8-in-one-day" regimen followed by either radiation after two cycles of chemotherapy versus craniospinal irradiation 1 year after diagnosis and completion of maintenance chemotherapy. Forty-six children with medulloblastoma were less than 18 months old. The 3-year PFS was 22% (± 6%). Thirty percent were alive and disease-free at a mean follow-up of 72 months.[40] The poorer outcome in the "8-in-one-day" regimen is probably best explained by the less intensive chemotherapy regimen in this study compared to the Baby-POG I trial. One of the largest trials for young children from the CCG (CCG 9921) reported on 92 children younger than 3 years of age, of which 61 patients had no evidence of metastasis by time of diagnosis. Children were treated with two different induction schemes followed by 8 cycles of maintenance chemotherapy. Children with no residual tumor after induction therapy and no metastasis at diagnosis did not receive radiation therapy unless they had evidence of recurrence. The EFS in the nonmetastatic group was 41% in 38 patients with GTR and 26% in 23 patients with residual tumor. In 31 patients with metastatic disease the EFS was 25%.[41] The Head-Start I study was designed to avoid radiotherapy. After GTR and induction chemotherapy with cisplatin, vincristine, etoposide, and cyclophosphamide, the patients underwent myeloablative consolidation chemotherapy with

carboplatin, thiotepa, and etoposide, and autologous stem cell rescue (ASCR). Two-year EFS and OS was 38% and 62%, respectively.[42] The induction chemotherapy was intensified during the Head Start II protocol by addition of methotrexate, which showed promising results. In this study, 9 children less than 3 years of age with disseminated medulloblastoma showed treatment response (8 with complete response and 1 child with partial response).[43] The Head Start III protocol is currently investigating the role of oral etoposide and temozolamide (TMZ). Current studies include standardized neuropsychological evaluations in comparison to questionnaires and parent interviews, which will be important in evaluating quality of life and long-term treatment side effects.

In summary, the optimal treatment for patients less than 3 years of age presenting with medulloblastoma has yet to be established. Promising results with intensified induction chemotherapy followed by high-dose chemotherapy with ASCR might justify further evaluation of these regimens, despite significant toxicity. Given the relatively low frequency of very young children with medulloblastoma, only international collaborations will lead to robust assessments of efficacy, quality of life, and neurocognitive outcomes of different treatment strategies.

Supratentorial primitive neuroectodermal tumors

Introduction. sPNETs consist of a heterogeneous group of highly malignant tumors arising at various locations within in the CNS but exhibit similar histology. sPNET account for only 1 to 2.5 % of all childhood tumors.[44,45] The mean age of onset is around 3 years of age and these tumors carry a very poor prognosis with a 5-year OS of usually less than 30%. Ongoing controversy exists if these tumors should be classified based on their location, pattern of differentiation, or if they should be seen as a single entity, which can arise throughout the CNS. As previously outlined, molecular studies revealed significant differences between sPNET and medullolastoma supporting the fact that at least infra- and supratentorially located PNETs are different entities. Commonly accepted poor prognostic factors are young age at presentation and evidence of dissemination. Metastasis outside the CNS is exceedingly rare and occurs in less than 0.5 % of patients.[46] The Chang classification system is commonly used for staging.[47] Overall sPNETs have a worse outcome and respond less to current therapy regimens compared to medulloblastomas.

Surgery

Surgical resection remains the mainstay of initial therapy in patients presenting with sPNET. To what extent GTR or near GTR has a positive influence on survival remains controversial.[48–52] The CCG-921 trial showed a better trend regarding outcome for patients with residual disease less than 1.5 cm^2, which did not achieve statistical significance possibly due to the small number of centrally reviewed patients.[48] A review of 22 patients with sPNET reported a 5-year PFS of 53% for patients who underwent GTR compared with 25% of those who only underwent partial resection or biopsy.[52] An analysis of patients treated in Italy with chemotherapy and hyperfractionated accelerated radiation therapy demonstrated that patients with GTR had a PFS of 83% (± 15%) versus 32% (± 18%) in patients with residual disease after surgery. However, due to the small sample size, this did not reach statistical significance.[53] In the HIT 88/89 and 91 trials patients with incomplete resection fared as well as those with GTR.[54] This is in concordance with a retrospective analysis from Canada that reported OS was not affected by the initial degree of surgical resection.[46]

In summary, surgical resection remains the standard of care for patients with sPNET, but to what degree the extent of resection matters remains controversial. The available information is limited to date, and further trials are needed to readdress the role of aggressive surgery given the associated morbidity.

Radiation therapy

Radiation therapy plays an important role in the treatment regimen for children with sPNET. Given the low incidence rate of these tumors, most of our current knowledge derives from subset analysis of larger trials or retrospective single institution experiences. Dosing, timing, and target volume of radiation continues to be subject of debate, but few conclusions can be drawn based on existing data. As previously outlined, the young patients (less than 3 years of age) are especially at high risk to develop adverse reactions to radiation therapy. The relative high percentage of young children presenting with sPNET makes the evaluation of treatment failure versus inherited differences in the tumor biology difficult, given that these patients often receive limited amounts of radiation. In 1990, the French Society of Pediatric Oncology (SFOP) pilot study was initiated as a trial to treat children less than 5 years of age with brain tumors (excluding gliomas) with postoperative conventional chemotherapy to delay radiation therapy. Twenty-three children were diagnosed by central review with sPNET, along with two additional parallel review cases that were included in the analysis. The OS was documented at 1, 2, and 5 years with 48%, 29%, and 14%, respectively. The authors concluded that postoperative chemotherapy without radiation is not adequate for the treatment of children with sPNET.[55] The German trials HIT 88/89, and HIT 91, revealed important information regarding the benefit of radiotherapy. A total of 63 patients with sPNET were treated with adjuvant chemotherapy in these studies. The 3-year PFS for children

treated with radiotherapy, according to guidelines was 49.3%, whereas children with major treatment violations regarding radiation therapy achieved a 3-year PFS of only 6.7%.[54] A recent retrospective analysis from Canada investigated outcome in 48 patients treated between 1995 and 2005 for sPNET. The 4-year survival was 37.7 % (± 7.6%) with a median follow-up of 42 months. The only independent significant factor associated with improved outcome was the use of radiation therapy.[46] A recent analysis from the University of California, San Francisco revealed that patients who received upfront radiation therapy have longer OS, as well as PFS.[56]

In summary, treatment for children greater than 3 years of age with sPNET consists of surgical resection followed by radiation therapy. Currently, the dose for craniospinal irradiation ranges from 23.4 Gy to 36 Gy, and the suggested tumor dose is between 54 Gy and 56 Gy.

Chemotherapy

The devastating side effects of radiation therapy led to multiple studies investigating different chemotherapy regimens to improve outcome. One landmark study by the COG demonstrated that patients older than 18 month (17 patients) with sPNET in the pineal region treated with chemotherapy ("8-drugs-in-1-day" or a combination of vincristine, lomustine, and prednisone) and craniospinal irradiation had a PFS at 3 years of 61% (± 13%), which was superior than prior published results. All infants in this study (8 patients) that were only treated with chemotherapy ("8-drugs-in-1-day") had progressive disease at a median of 4 months.[57] In the HIT 88/89, and HIT 91, studies the treatment with pre-irradiation chemotherapy (ifosfamide, etoposide, methotrexate, cisplatin, and cytarabine) or chemotherapy after irradiation (cisplatin, vincristine, and lomustine) did not correlate with improved outcome.[54] The SFOP demonstrated that chemotherapy (composed of carboplatin/procarbazine, etoposide/cisplatin, or vincristine/cyclophosphamide) without radiation is not sufficient for the treatment of sPNET and that foregoing radiation therapy worsens outcome.[55] Duke University treated 6 children and 6 adults with pineoblastoma with cyclophosphamide-based induction chemotherapy, radiotherapy, and high-dose chemotherapy with cyclophosphamide and busulfan or mephalan followed by ASCR. Ten of 12 patients received craniospinal irradiation (36 Gy) and a local boost to the pineal area (range, 55.2 to 66 Gy). At a median follow-up of 62 months, nine patients were alive including three patients with metastatic disease and two infants who never received radiation therapy. The authors concluded that high-dose chemotherapy is effective in patients with pineoblastoma and should especially be considered as initial treatment in infants and patients with metastatic disease.[58] The PNET 3 study enrolled 68 patients with sPNET. These patients were treated with either a combination of chemotherapy (vincristine, etoposide, carboplatin, and vincristine, etoposide and cyclophosphamide) and radiation therapy (44 patients) or just radiation therapy (24 patients). The 3-year and 5-year OS in the combination group was 52.3% and 45% respectively, compared with a 3-year and 5-year OS of 58.3 % and 54.2%, respectively, in patients just treated with radiation therapy.[59] A combined analysis of 17 patients enrolled in the CCG 9883 and MSKCC-89-173 trials investigated high-dose chemotherapy (combination of thiotepa, etoposide, with or without carboplatin) with ASCR specifically for patients with recurrent sPNET. Ten patients experienced tumor relapse at a median of 160 days after ASCR and died. Almost all surviving patients (4 of 5) underwent radiation therapy and had no evidence of measurable tumor prior to irradiation. Given the small sample size, it is impossible to determine which treatment contributed in these patients to their favorable outcome.[60] The Head Start I and II protocols investigated the role of intensive chemotherapy with ASCR in patients with newly diagnosed sPNET (43 patients). The 5-year OS was 49%. Over half of the surviving patients (12 of 20) remain alive without radiation exposure and 15 of 20 had no craniospinal irradiation.[61] Again, given the two different treatment regimens in these two protocols it remains difficult to answer which part of the therapy was most beneficial. Chintagumpala et al.[62] investigated the use of reduced craniospinal irradiation (23.4 Gy) and high-dose chemotherapy with ASCR in children with nonmetastatic sPNET. In this study, patients with high-risk disease (defined as having either residual tumor >1.5 cm^2 or evidence of metastatic disease) received 36.0 to 39.6 Gy, and those with average risk disease only 23.4 Gy to the craniospinal axis. High-dose chemotherapy consisted of four cycles of cyclophosphamide, cisplatin, and vincristine. Of 16 patients, 12 are alive at a median follow-up of 5.4 years. The-5 year EFS estimates were reported for average disease-risk patients at 75% (± 17%) and for high-risk patients at 60% (± 19%). These results are comparable with other studies and suggest that reduced craniospinal irradiation in combination with chemotherapy in average-risk patients might not compromise outcome.[62]

The information available today suggests that sPNETs are chemo-sensitive and that high-dose chemotherapy can be successfully used in newly diagnosed sPNET. Especially younger children (<3 years of age) might benefit from high-dose chemotherapy with ASCR as initial therapy to delay radiation therapy.

Future directions for medulloblastoma/sPNET

Major advances have been accomplished over the last few years especially for children with average risk medulloblastoma. Comparison between treatment trials, however, remains challenging, given the heterogeneity

Table 1. *Summary of Clinical and Molecular Markers Associated with Poor and Favorable Outcome in Medulloblastoma*

	Poor Outcome	Favorable Outcome
Clinical parameters	Age <3 years	Age <3 years
	Residual disease >1.5 cm^2 after resection	Complete resection
	Metastasis	
Molecular markers	p17 chromosome loss	TRK C expression
	1q chromosome gain	Wnt/wingless pathway activation and loss of chromosome 6
	8q chromosome gain	
	C-myc expression	Beta-catenin expression
	Erb B2 receptor expression	
	P53 expression	
	Survivin expression	
	EEF1D, RPL30, RPS 20 expression	
	OTX2 overexpression and amplification	

Erb B2 = epidermal growth factor receptor B2; EEF1D = eukaryotic translation elongation factor 1; RPL30 = ribosomal protein l30; RPS20 = ribosomal protein S20.

of these tumors, especially for sPNET. Advances in understanding the molecular profile and associated clinical outcome will eventually lead to better risk stratification and enable treating neuro-oncologists to better determine risk-benefit profiles for each individual patient. The benefit of gene expression analysis of tumors to predict clinical outcome has already been established.[63] Further, several markers have been linked to prognosis (Table 1). For example activation of the Wnt/beta catenin pathway and high expression of tyrosine receptor kinase C is associated with favorable outcome,[64–67] whereas c-myc expression has been linked to poor outcome in multiple studies for patients with medulloblastoma.[68–71] Overexpression of the homebox gene *OTX2* is associated with anaplastic histological features in medulloblastoma, which is amplified in a subset of medulloblastomas.[72] Integration of molecular studies in larger multicenter trials will be pivotal to enhance our understanding and to identify new therapeutic targets. To date, very little is known about the molecular biology of sPNET, but several key signaling pathways have been identified in medulloblastomas. These include the wingless, sonic Hedgehog and Notch pathways. Inhibition of these signaling cascades with small molecules led in different *in vivo* and *in vitro* models to regression of tumors and represent new attractive therapeutic avenues.[73–75] More recently it appears the activation of the phosphatidylinositol-3-kinase pathway might be associated with medulloblastomas. Therefore, phosphatidylinositol-3-kinase inhibitors may be attractive candidates in the treatment of these tumors.[76–78] Preclinical studies have shown that retinoic acid (RA) has anticancer activity in a variety of cancers and is commonly used in acute promyelocytic leukemia and high-risk neuroblastoma. *In vitro* studies have shown that RA can also induce apoptosis in medulloblastoma cell lines.[79] Subsequently, *in vivo* studies have demonstrated that a combination of RA with the histone deacetylase inhibitor suberoylanilide hydroxamic acid is effective in medulloblastoma xenografts as well as in transgenic mice.[80] Currently, RA is tested in clinical studies for children with medulloblastoma (Table 2).

The main goal for patients with average-risk disease is to improve morbidity of current treatment regimens and maintain adequate survival. Ongoing studies aim to reduce the amount of radiation exposure by using different radiation regimens like hyperfractionated accelerated radiation therapy and proton beam therapy in combination with chemotherapy including ASCR. For patients with high-risk and recurrent disease, survival remains poor; therefore, improving outcome is the focus of current investigations. Currently, different combinations of chemotherapy as well as radiation therapies are being tested. Newer approaches including intrathecal radio-immunotherapy and different small molecule inhibitors are also of exploratory interest. Table 2 lists a selection of ongoing clinical trials for newly diagnosed patients and patients with recurrent/refractory disease.

Astrocytomas

Astrocytomas are the most common subtype of pediatric brain tumors representing more than 50% of all tumors. The World Health Organization (WHO) classifies these tumors into low-grade (grade I-II) and high-grade (grade III-IV) tumors. Largely, the cause remains unknown, although some genetic disorders such as neurofibromatosis 1 or Li-Fraumeni syndrome carry a higher risk to develop these tumors. Prior radiation to the brain also remains a known risk factor. The outcome is correlated with histological grade, and survival remains poor in patients with high-grade astrocytomas.

High-grade astrocytomas

Introduction. High-grade gliomas are classically divided into WHO grade III tumors of anaplastic astrocytomas, WHO grade IV tumors of glioblastoma multiforme (GBM), and WHO grade III tumors of anaplastic oligodendroglial or mixed astrocytic tumors, which are less commonly found in children. High-grade gliomas

Table 2. *Ongoing Clinical Trials for Patients with Newly Diagnosed or Refractory/Recurrent Medulloblastoma/sPNET*

Indication/Goal	Phase	Conventional Chemotherapy	Radiation Therapy	Investigational Agent	Molecular Biology
Newly diagnosed medulloblastoma/sPNET					
Two different RT regimens in combination with ASCR	III	CS, CP, V with ASCR	+ two different RT regimens	—	Erb B2 expression; protein/mRNA expression
Low-dose RT with chemotherapy	II	CS, CP, ET, L, V	CIS 18 Gy	—	—
Low-dose RT compared with standard dose RT with combination chemotherapy	III	CS, CP, L, V	CIS 18 Gy vs standard; tumor boost vs posterior fossa	—	—
Compare different chemotherapy regimens prior to ASCR in children <36 month	III	CB, CS, CP, E, T, V, MTX	—	—	—
Proton beam radiation	II	—	Proton beam CSI and posterior fossa	—	—
Different chemotherapy and radiation therapy regimens	III	CB, CS, CP, V	Standard XRT	Isotretinoin	—
Radioimmunotherapy, reduced-dose EB-CSI with IMRT boost and chemotherapy	II	CP, L, V	EB-CSI with IMRT boost	I^{131} 3FA	—
Recurrent/Refractory medulloblastoma/sPNET					
Hedgehog antagonist (GDC-0449)	I	—	—	GDC-0449	Gene expression analysis
Notch Signaling inhibitor (MK 0752)	I	—	—	MK 0752	—
Angiogenesis inhibitor Bevacizumab	II	Irinotecan	—	Bevacizumab	—
VEGF inhibitor Cediranib (AZD 2171)	I	—	—	Cediranib (AZD 2171)	—

ASCR = autologous stem cell rescue; CB = carboplatin; CP = cyclophosphamide; CS = cisplatin; CSI = craniospinal irradiation; E = etoposide; EB-CSI = external beam CSI; Erb B2 = epidermal growth factor receptor B2; IMRT = intensity modulated radiotherapy; L = lomustine; RT = radiation therapy; SPNET = supratentorial primitive neuroectodermal tumors; V = vincristine; VEGF = vascular endothelial growth factor.

make up the minority (up to 20%) of supratentorial tumors in children.[45] The 5-year survival rate ranges from 5 to 15% for GBM and 20 to 40% for anaplastic astrocytomas.[81] Diffuse brain stem gliomas are characteristically grade III or IV tumors and will be discussed separately as follows.

Current treatment strategies

Surgery. Surgical resection remains the cornerstone for the treatment of children with high-grade gliomas. Multiple studies have shown that the extent of resection is strongly linked to survival and therefore GTR is favored.[82–85] For example, children with high-grade gliomas treated in the CCG 945 study who underwent GTR demonstrated a 5-year PFS of 35% (± 7%) compared with 17% (± 4%) in patients who underwent STR.[84] This correlation was also found in the subgroup analysis of patients with anaplastic astrocytomas (GTR: 5-year PFS 44% [± 11%] compared to STR: 5-year PFS 22% [± 6%]), and GBM (GTR: 5-year PFS 26% [± 9%] compared to STR: 5-year PFS 4% [± 3%]).[84] However, one hallmark of high-grade gliomas is their infiltrative growth pattern that makes it difficult to obtain clear tumor boundaries. If the tumor extends into critical areas of the brain or crosses the midline, then an attempt should be made to remove as much tumor as is safely possible.

Radiation

Radiation therapy has been the standard of care for many years for patients with high-grade gliomas. It is generally recommended after surgery for children greater than 3 years of age. Studies have shown that most high-grade gliomas reoccur within a 2-cm margin of the original tumor location. Therefore, radiation is mainly aimed at the primary tumor site with a small margin. Common treatment regimens are composed of 50 to 60 Gy of external beam radiation delivered in daily fractions of 180 to 200 cGy. Higher radiation doses (to a cumulative total dose of 72 Gy) in conjunction with hyperfractionation have failed to improve outcome for patients with high-grade gliomas.[86]

Chemotherapy

One of the first randomized trials (CCG 943) that investigated the role of chemotherapy in 72 children with high-grade gliomas was conducted by the CCG from 1976 until 1981.[87] The investigators reported a 5-year

EFS of 46% in patients who received radiation and chemotherapy (nitrosourea, vincristine, and prednisone) compared with a 5-year EFS of 18% in patients who only underwent radiation therapy after surgical resection.[87] Surprisingly, the effect of chemotherapy was strongest in patients with GBM. In this subgroup, 5-year EFS was 42% in the combined group compared with 6% in patients just receiving radiation therapy.[87] A subsequent large phase III study (CCG 945) showed that a more intense chemotherapy with the "8-in-one-day" regimen versus the prior tested regimen with lomustine, vincristine, and prednisone had no beneficial effect on survival. Further analysis of the CCG-945 study showed that a significant number of patients were misclassified by institutional review and revised by a consensus neuropathology review as low-grade tumors.[88,89] This is critical when assessing outcome of other treatment trials, and it highlights the importance of a central review process in pediatric gliomas. Since then, multiple trials investigated different chemotherapy regimens for the treatment of pediatric high-grade gliomas. The HIT-91 trial randomized children to either a sandwich therapy consisting of pre-irradiation chemotherapy (ifosfamide, VP-16, methotrexate, cisplatin, and cytarabine) followed by radiation therapy compared with radiation therapy followed by chemotherapy (lomustine, vincristine, and cisplatin). The multivariate analysis showed that pre-radiation chemotherapy, grade III tumors, and GTR (defined as >90% resection) were associated with improved survival. The median OS was 5.17 years for the sandwich arm compared with 1.94 years for the maintenance arm.[85] In the CCG-9933 study, the investigators compared three different alkylating agents (carboplatin, ifosfamide, and cyclophosphamide) administered in conjunction with etoposide in patients with residual disease. Unfortunately, none of the three treatment arms showed beneficial effect toward survival.[90] The SFOP treated high-grade glioma patients with limited success with a combination of carmustine, cisplatin, and etoposide after surgery. The 5- and 10-year OS were reported at 16% (± 9%) and 13.3% (± 9.4%), respectively.[91] Concomitant TMZ and radiation therapy is the current standard for adult GBM patients. Multiple studies tested the response of pediatric high-grade gliomas and recurrent high-grade gliomas to TMZ with limited success.[92–94] The difference in response to TMZ highlights the fact that pediatric high-grade gliomas are biologically different from their adult counterpart, despite similar histology. To date, most children with high-grade gliomas are enrolled in clinical trials, and the most effective chemotherapy regimen still needs to be established.

Future directions

Adult high-grade gliomas have been intensely studied, and key molecular pathways (e.g., the epidermal growth factor receptor [EGFR] pathway) have been identified to play a major role in the tumorigenesis of these tumors. Furthermore, targeted therapy against angiogenesis with, for example, bevacizumab (an antibody directed against vascular endothelial growth factor [VEGF]), has shown encouraging results in adult gliomas.[95] Our current knowledge about key signaling cascades involved in pediatric gliomas remains limited. Inhibitors of EGFR or platelet-derived growth factor receptor are tested in phase I/II trials with and without radiation, as well as in combination with conventional chemotherapy. Erlotinib, an EGFR inhibitor, has recently been tested in a phase I trial in combination with radiation. One-year PFS was reported at 56% (± 10%) and 2-year PFS at 40% (± 13%).[96] A recent phase I study from COG showed that the combination of erlotinib and TMZ is safe in children, and further studies are needed to assess tumor response.[96] Imatinib, a platelet-derived growth factor receptor inhibitor, has been associated in a phase I trial with increased incidence of intracranial hemorrhage, especially in patients with brainstem gliomas. Although survival analysis was not primary objective of that study, estimates of PFS was not superior to other studies.[97] Other small molecule inhibitors currently under investigation include inhibitors of the farnesyltransferase (lonafarnib), Notch (MK 0752) and mammalian target of rapamycin ([mTOR] temsirolismus, everolismus) signaling pathways as well as anti-angiogenic agents like bevacizumab. These agents are tested as single agent, as well as in combination with conventional chemotherapy and radiation. Antibody- or ligand-mediated targeting of tumor cells, vaccine therapy, and radionuclide conjugates specifically designed to bind directly to tumor cells are other avenues, which are currently explored for the treatment of high-grade gliomas.

Low-grade astrocytomas

Introduction. Low-grade astrocytomas account for approximately 40% of all childhood CNS tumors. Histologically low-grade gliomas are mainly classified into pilocytic astrocytomas (WHO grade I, also known as juvenile pilocytic astrocytoma) and fibrillary astrocytomas (WHO grade II), although other subgroups (such as gemistocytic astrocytomas or pleomorphic xantho-astrocytoma) have also been described. The most common location for juvenile pilocytic astrocytoma is the cerebellar hemispheres. Cerebellar astrocytomas present 20 to 35% of all posterior fossa tumors. The majority of these tumors (80%) are juvenile pilocytic astrocytomas, followed by grade II (15%) tumors. Other subtypes based on location are hemispheric, optic pathway, and thalamic lesions with distinct clinical features. Overall these tumors have a very good prognosis with 5-year OS rates of 80 to 90%.

Current treatment strategies for low-grade astrocytomas

Surgery. The first line treatment for children with low-grade gliomas is GTR. The extent of resection is strongly correlated with survival.[98–100] In one series 10-year PFS was 100% in patients with GTR compared with only 67% in patients with STR.[99] With the introduction of neuro-navigation systems, functional brain mapping via functional MRI, positron emission tomography, magnetoencephalography (an imaging technique that measures noninvasively the electrical activity in the brain that can be overlaid with MRI images), and cortical mapping, even lesions located in eloquent brain areas become more accessible for resection with minimal surgical morbidity. Given the relative indolent course of most low-grade gliomas, residual tumors are often followed by serial imaging. Second-look surgery is a viable option in case of recurrence or progression.[99,101,102] Cerebellar astrocytomas, mainly consisting of grade I and II astrocytomas histologically, are curable by GTR. Recurrence-free survival is greater than 95% at 10 and 20 years.[103] Many childhood low-grade gliomas extent to deep midline structures, which makes a GTR extremely difficult and are therefore associated with worse outcome.[103] A common tumor in patients with neurofibromatosis 1 is a low-grade glioma of the optic pathways. Several studies have shown that optic pathway gliomas in neurofibromatosis 1 patients have a more indolent course and can be followed with serial imaging only. Surgical resection is not indicated in most cases unless there is evidence of tumor progression.[104]

Radiation

Generally patients with low-grade gliomas who undergo complete resection are not treated with adjuvant therapy until there is evidence of disease recurrence or progression on surveillance imaging. Patients treated on the CCG 945 trial, who were subsequently re-classified as low-grade tumors, showed a 5-year PFS of 68% (± 6%) when treated with radiation therapy in conjunction with chemotherapy compared with only 38% (± 12%) when undergoing just chemotherapy. OS however, was not significantly affected by radiation therapy (5-year OS for chemo-radiotherapy group 79% [± 3%], compared with 77% [± 10%] for the chemotherapy-only group).[105] The experience at University of California, San Francisco demonstrated that upfront radiation therapy for patients with grade II gliomas did not improve survival, even in the setting of STR. This retrospective analysis of 90 patients revealed again the importance of the extent of resection on OS.[106] Stereotactic radiation for localized disease has also been studied. One study demonstrated a 5-year OS of 97.7% and 8-year OS of 82% for children treated with stereotactic radiation therapy after evidence of recurrence or progression on chemotherapy or just after surgery alone.[107] To date, the role of radiation in the treatment of low-grade gliomas has not been established and further studies are indicated.

Chemotherapy

Chemotherapy has been used for many years in different regimens for the treatment of patients with low-grade gliomas after subtotal resection or evidence of progressive disease. The heterogeneity of this tumor group, however, makes it difficult to compare results. In 1993, Packer et al.[108] reported a radiographic response in 52% of patients with recurrent disease and 62% in newly diagnosed patients treated with vincristine and carboplatin. These results were reproducible in a larger follow-up study of patients with newly diagnosed tumors.[109] Currently, vincristine in combination with carboplatin is the most commonly used multi-agent chemotherapy for children with low-grade gliomas and future trials will be judged against these results.[110] Over one tenth of children treated with carboplatin and vincristine will develop allergic reactions to carboplatin that often require cessation of therapy, and therefore new reagents are under investigation.[108] Patients with recurrent or progressive low-grade gliomas treated with cisplatin and etoposide showed an objective response rate in 70% (24 of 34 patients).[111] TMZ has been tested in pediatric low-grade glioma with moderate success.[112,113] One study treated 30 children with progressive or recurrent low-grade gliomas with TMZ orally on 5 consecutive days (dose, 200 mg/m^2). Treatment cycles were repeated every 28 days and ranged from 2 to 12 cycles. The majority of patients in this study (19 of 30) were treated with chemotherapy and/or radiation therapy prior to enrollment. The 4-year PFS and OS were 17% (95% CI, 1 to 33%) and 71% (95% CI, 43 to 100%), respectively. Partial or minimal response was only observed in 12% of the patients. Only 9 patients (30%) had stable disease and did not require any additional treatment after TMZ therapy. Eighteen patients required salvage therapy. The outcome compares unfavorably to prior reports as previously outlined.[58] Ongoing studies are currently investigating the best chemotherapy regimen for these patients.

Future directions for low-grade gliomas

Genetic alterations frequently observed in adult anaplastic astrocytomas and/or glioblastomas, such as mutations of *TP53* or *PTEN*, homozygous deletion of *CDKN2A*, amplification of *CDK4* or EGFR, and losses of chromosome 10, are only rarely encountered in pediatric pilocytic and low-grade diffuse astrocytomas.[114] Most of these low-grade gliomas in children also show no significant change in copy number and have normal karyotypes,[115–117] but one consistent finding between studies was the identification of trisomy of chromosome 5 and 7 or gains of 1q.[117–119] The mitogen-activated protein kinase pathway activation in low-grade gliomas

has been described in several studies and recently linked to duplication of the *BRAF* gene locus.[120] Thus, aberrant mitogen-activated protein kinase signaling appears to be of importance in the pathogenesis of low-grade astrocytomas, and pharmacological inhibition of this pathway may constitute a promising new approach in the treatment of these tumors.[120–122]

Given the relative benign nature of low-grade gliomas and good OS, the focus of current studies is to avoid morbidities from medical treatment. Therefore, the goal is to minimize radiation exposure especially in young children due to the known adverse side effects. The best treatment strategy for recurrent or progressive low-grade gliomas is still under investigation, and currently different chemotherapy and radiation regimens are tested in clinical trials as listed in Table 3. The heterogeneity of low-grade gliomas makes interpretation of these studies difficult, and further attention needs to be directed in identifying key genetic and molecular characteristics.

Diffuse brain stem glioma

Introduction. Diffuse brainstem gliomas account for 58 to 75% of all pediatric brainstem tumors. They are characteristically malignant fibrillary astrocytomas (WHO grades III and IV), although other entities have been reported.[123–126] The long-term survival is very poor with only 6 to 10% of patients surviving beyond 2 years of age, which has not changed over the last decades.[127] Historical control data are relatively homogeneous among several trials and reveal 1-year OS of 30% (± 3%) and 1-year PFS of 12% (± 2%), which against new therapeutics avenues will be tested.[128]

Current treatment strategies

Surgery. Surgical intervention has a limited role in the management of diffuse brainstem gliomas because MRI is generally sufficient to establish the diagnosis,[129] and meaningful resection remains impossible due to the diffuse infiltration of the tumor in surrounding brainstem structures.[130] A biopsy can be performed safely if needed, but often does not alter the therapeutic approach and is generally not recommended.[124] For example, the CCG investigated the role of biopsy in a total of 120 children with diffuse brainstem gliomas. Of these, 45 children underwent biopsy with pathology available in 36 cases (low-grade astrocytoma [13], anaplastic astrocytoma [20], GBM [2], nondiagnostic [1]). Regardless of pathology or whether a biopsy was performed, all patients had a poor outcome.[131] To date, most centers diagnose children with diffuse brain stem gliomas based on characteristic MRI findings in the right clinical scenario without tissue diagnosis.

Radiation

Radiotherapy remains the cornerstone for the treatment of diffuse brain stem glioma, but it is not curative. Most patients show an initial response to therapy, but usually within a few months the tumor progression occurs. Multiple studies investigated the benefit of escalating the radiation dose through hyperfractionation with disappointing results. The POG compared doses up to 7560 cGy and demonstrated that there was no significant survival benefit with higher doses of radiation.[132] The CCG used 7,800 cGy and found similar results.[131] Radiosensitizing agents like cisplatin have been tested with conventional versus hyperfractionated accelerated radiation therapy with no survival benefit for the latter group.[133] The current standard of care for diffuse brainstem gliomas is conventional radiotherapy with a local field dose of 5,400 to 6,400 cGy in 6 weeks in 180 cGy daily fractions, but outcome remains poor.

Chemotherapy

Given the dismal outcome for patients with diffuse brainstem glioma, many studies have investigated the role of different chemotherapy regimens for the treatment of these patients, but currently the added benefit remains a subject of debate. One study conducted by the CCG compared the effect of irradiation with and without two different adjuvant chemotherapy regimens composed of carboplatin, etoposide, vincristine or cisplatin, etoposide, cyclophosphamide, and vincristine. There was no significant improvement with the addition of either chemotherapy regimen.[134] The POG demonstrated that children treated with radiation therapy alone had similar outcome to patients treated with radiation and cisplatin.[135] Marrow ablative chemotherapy with ASCR has been investigated in patients newly diagnosed or with

Table 3. *Selection of Ongoing Clinical Trials for Children with Low-Grade Gliomas*

Indication	Phase	Conventional Chemotherapy	Radiation Therapy	Investigational Agent	Molecular Biology
Progressive LGG	II	Vinblastine	—	—	—
Progressive LGG	II	Everolismus	—	—	—
Progressive LGG to assess RT versus CT	III	CB, CS, E, V	RT	—	—
Progressive LGG	I/II	Irinotecan	—	Erlotinib	EGFR
LGG	III	—	Stereotactic vs. conventional RT	—	—

CT = chemotherapy; EGFR = epidermal growth factor receptor; LGG = low-grade glioma; RT = radiation therapy.

recurrent disease with no significant benefit on survival, but with significant toxicities.[136–138] Most recently a small study assessed the benefit of neoadjuvant chemotherapy (cisplatin, methotrexate) to delay radiation therapy until time of progression. The results were compared with a historical cohort and demonstrated a median survival of 17 months in the treatment group compared with 9 months in the control group, but therapy was associated with significant toxicity and prolonged hospitalizations.[139] TMZ in combination with cis-retinoic acid and radiation therapy has been tested in a small number of patients with brain stem glioma with limited success and a reported median survival of 13.5 months (± 3.6 months).[140] One difficulty in assessing the benefit of different chemotherapy regimens is the inconsistency between trials regarding eligibility criteria, assessment of tumor progression, and different endpoints. However, despite this variability, no improvement in survival has been documented for the last 30 years.[141] Because the outcome has not been changed, despite multiple different avenues investigated, these patients should be considered for phase I trials whenever possible.

Future directions

Progress in the development of effective therapies for diffuse brainstem glioma is compromised by the unavailability of tissue samples and the lack of noninvasive markers that can characterize disease status. Conventional MRI has been shown to be insufficient in predicting clinical outcome.[142] The limited information currently available on molecular pathways involved in the tumorigenesis of these tumors limits a rational approach to test new agents. To date, new trials are often designed based on knowledge gained from other adult or pediatric high-grade glioma experiences. Inhibitors of EGFR (e.g., gefitinib or erlotinib) have been tested in diffuse brain stem gliomas in small series with minimal success.[143,144] Inhibition of angiogenesis is another focus of current investigations. Bevacizumab showed promising results in adult patients with high-grade glioma, and is currently studied in pediatric brainstem gliomas.[95] Other anti-angiogenic agents currently under investigation include the oral VEGF inhibitor AZD2171. Another research area is the delivery of agents to the tumor, either by catheter-based technologies, such as convection-enhanced delivery, or with the use of small molecules interrupting the blood brain barrier.[145]

Ependymoma

Introduction. Ependymoma is the third most common pediatric brain tumor after astrocytomas and medulloblastomas. The peak incidence is between birth and 4 years of age.

Currently, ependymomas are classified by the WHO as grade I (myxopapillary), grade II (cellular, papillary, clear cell, and tancytic), and grade III (anaplastic), although clinical studies have failed to show a correlation between grade and overall outcome.[146] The high variability among neuropathologists with reported discordance of 69% between central and local review remains a challenge in developing new therapeutics and assess the response rates in different clinical trials.[147,148] In a recent analysis of a population-based registry, 5-year OS was reported to be 57.1% (± 2.3%). Infratentorial location was associated with improved 5-year OS (86.7 % ± 5.2%) compared with supratentorially located tumors (5-year OS 59.5% [± 5.5%]).[149]

Current treatment strategies

Surgery. Surgical resection remains the mainstay of initial management and multiple studies have linked outcome to the extent of resection.[148,150] The German HIT trial demonstrated that the only two significant prognostic factors were the extent of resection with a 3-year PFS of 83.3% after GTR compared to 38.5% after STR, as well as the presence of metastases at the time of diagnosis.[150] In a prior study, patients undergoing GTR had a 5-year PFS of 66% compared with 11% without complete resection.[148] Second-look surgery should be considered in patients with residual disease because the majority of recurrence occurs at the primary tumor site.

Radiation therapy

Radiation therapy is considered by many the standard of care for intracranial ependymomas in children older than 3 years of age. Multiple studies have shown adequate control with radiation targeted to the initially involved area.[151–153] The experience from St. Jude's hospital demonstrated a 3-year PFS of 69.5% in a phase II trial using conformal radiotherapy in 88 children with ependymoma (55% <3 years of age). Serial neurocognitive evaluations demonstrated no significant decline before and after radiation therapy independent of age.[152] A recent study reported promising results using proton beam radiation for patients with ependymomas. The major aim using proton radiotherapy is to reduce the amount of radiation exposure to normal brain. This is mainly achieved by elimination of exit dose and reduction of entrance dose. A total of 17 patients were evaluated and at a median follow-up of 26-month PFS reported at 80% (± 10%) and OS at 89% (± 10%).[154] The follow-up of this study is too short to determine the effect on long-term outcome. Prophylactic spinal irradiation did not seem to modify outcome in multiple series and should be reserved for patients with evidence of spinal seeding, and might be considered in patients with infratentorial anaplastic ependymomas.[155,156] Radiosurgery is a potential treatment option for patients with recurrent disease. In one study local tumor control was achieved in 3 of 5 patients treated for localized residual ependymoma.[157] A phase I study also demonstrated that intraoperative radiotherapy with photon radiosurgery might be an alter-

native treatment strategy for patients with recurrent disease. Of 14 patients (13 diagnosed with recurrent ependymoma), 8 (57%) showed local tumor control after surgical resection and intraoperative radiotherapy.[158] With the development of these new radiation techniques, the effect on cognition and development might be reduced and therefore become a valid part in the treatment of these patients, independent of age.

Chemotherapy

The role of chemotherapy in the treatment of ependymomas remains controversial. Given the relatively high number of patients who are less than 3 years of age at time of diagnosis, multiple studies have investigated the role of chemotherapy to delay irradiation and avoid the associated side effects. A study from the United Kingdom Cancer study group and International Society of Pediatric Oncology treated children less than 3 years of age with combined adjuvant chemotherapy (carboplatin, vincristine, cyclophosphamide, cisplatin, and methotrexate). Radiation therapy was reserved for patients with recurrent resistant disease. The authors reported a 3-year PFS of 69.5%, but 34 of 50 patients who had evidence of progression underwent subsequently radiotherapy.[159] These findings are better than prior reports from the POG, who treated patients from 1986 until 1990 with 12 or 24 months of chemotherapy prior to radiation with a disappointing 5-year PFS of 27%.[160] The French oncology group reported a 4-year PFS of 22% in 73 patients treated with chemotherapy only.[161] The CCG 9921 study assessed the effect of two different chemotherapy regimens in 74 children less than 3 years of age to estimate control intervals without irradiation.[41] Chemotherapy consisted of induction chemotherapy with vincristine, cisplatin, etoposide, and cyclophosphamide, or vincristine, carboplatin, ifosfamide, and etoposide. Maintenance chemotherapy was the same in the two treatment arms and compromised vincristine, etoposide, carboplatin, and cyclophosphamide. Radiation therapy was delayed in children with no residual or metastatic disease, unless they progressed. There was no significant difference between the two treatment arms. The 1- and 5-year PFS were 72% (± 5%) and 32% (± 6%), respectively for patients diagnosed with ependymoma. Five-year OS was 59% (± 6) and 63% of the 5-year event-free survivors had not received radiation therapy.[41] Multiple agents including carboplatin, cisplatin, etoposide, idarubicin, ifosfamide, irinotecan, carmustine, and TMZ have been studied in phase II trials with modest response.[162] Multi-agent strategies (e.g., lomustine, prednisone, and vincristine),[163] as well as high-dose chemotherapy with stem cell rescue have been disappointing and can not be generally recommended.[164] Chemotherapy to date is used as an adjuvant therapy in patients with residual or recurrent disease, but cannot be recommended as standard treatment.

Future directions for ependymomas

Molecular biology. Little is known regarding the molecular pathways involved in the development of ependymomas compared with other brain tumors. Loss of the tumor suppressor gene neurofibromatosis (NF) 2 on chromosome 22 has been frequently described in ependymomas.[165–167] NF2 is a key regulator of cell membrane/cytoskeleton-associated protein 4.1 super family. Other members of the same group (4.1 B and 4.1 R) have also been associated with ependymomas.[168] Through comparative genomic hybridization and gene expression analysis, common pathways associated with the development of cancer have been associated with ependymomas like the Notch, sonic hedgehog, and EGFR/phosphatidylinositol-3-kinase/Akt pathway.[169–171] Recent studies identified radial glial cells as the potential cancer stem cells of ependymomas.[171,172] If the stem cell hypothesis holds true, it will be essential for further drug development in particular to address these cancer stem cells.

Ongoing clinical trials

Current studies are testing investigational agents, combination chemotherapy, and different radiation therapy regimens for patients with ependymomas (Table 4). The benefit of anti-angiogenesis therapy with antibodies directed against VEGF is under current investigation in

Table 4. *Selection of Ongoing Clinical Trials for Children with Ependymomas*

Indication	Phase	Conventional Chemotherapy	Radiation Therapy	Investigational Agent	Molecular Biology
Recurrent/anaplasic ependymoma	II	TMZ	—	Lapatinib	—
Localized ependymoma	II	CP, E, V	If recurrent disease + RT	—	—
Residual ependymoma	II	MTX	—	—	—
Ependymoma in children <3 years of age	III	CB, CP, CS, MTX, V	When progression + RT	—	+
Ependymoma	II	Irinotecan	—	Bevacizumab	—

TMZ = temozolamide.

recurrent ependymomas. Only a limited number of studies to date include biological endpoints in the study protocol. Further characterization of the underlying signaling pathways will be important to develop new therapies and to better risk stratify patients with ependymoma.

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