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Chemotherapy for malignant brain tumors of childhood

Nicholas G. Gottardo and **Amar Gajjar**
Division of Neuro-Oncology, Department of Hematology-Oncology, St Jude Children's Research Hospital, 332 North Lauderdale St., Memphis, TN 38105, USA

Abstract

During the past 3 decades, chemotherapeutic agents have been extensively evaluated for the treatment of pediatric brain tumors in a myriad of schedules, doses, and combinations. Remarkable advances in outcome have been achieved for certain groups of children, notably those with medulloblastoma, and chemotherapy has played a key role. However, improvements in survival are obtained at a high cost to quality of life. In addition, the success achieved for medulloblastoma is offset by a lack of progress for high-grade glioma. Despite decades of intensive investigation, no single chemotherapeutic regimen stands out as particularly beneficial for children with high-grade glioma, with the vast majority of these patients succumbing to their disease. A plateau in efficacy has been reached. Further treatment intensification using conventional nonspecific chemotherapy is more likely to result in additional toxicity without major advances in survival. Genomewide analysis using microarray technology has contributed significantly to our understanding of tumor biology. This knowledge has shifted the focus onto novel agents that target molecular changes crucial for tumor proliferation or survival. These selective agents are likely to be less toxic to normal cells and it is anticipated they will be more effective than the nonspecific chemotherapeutic agents currently used.

Introduction

Brain tumors represent the second most common cancer and the most common solid tumor in childhood, accounting for 4.3 cases per 100,000 person-years in the United States.[1] The incidence peaks among children ages 3 to 7 years, although all ages are affected. In adults and older children, most tumors are located supratentorially; in young children CNS tumors are more commonly infratentorial.

The improved outcome for children with medulloblastoma represents a success story for pediatric neuro-oncology. Five decades ago children diagnosed with medulloblastoma faced almost certain death. Today, treatment that includes surgical resection, craniospinal irradiation (CSI), and chemotherapy cures approximately 80% to 85% of children diagnosed with average-risk medulloblastoma[2,3] and up to 70% of those classified with high-risk disease.[2] However, these remarkable improvements in survival are obtained at a high cost to quality of life. Many survivors experience significant long-term neurocognitive[4–6] and neuroendocrine effects.[7] Intriguingly, these advances in outcome have been achieved through the systematic use of empirically based treatment regimens, including CSI and chemotherapy, not through increased understanding of tumor biology and novel therapies.

Corresponding author: Amar Gajjar, MD, St. Jude Children's Research Hospital, Mail Stop 260, 332 North Lauderdale Street Memphis, TN 38105, Tel: (901) 495-5898, Fax: (901) 521-9005.

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In stark contrast, little progress in survival has been made for children with high-grade gliomas. In spite of modern aggressive multimodality therapy, including surgery, radiotherapy (RT), and chemotherapy, survival remains very poor, with 2-year progression free survival (PFS) less than 20%.[8] The role of maximum safe surgical resection and RT are well-established in the treatment of pediatric high-grade glioma. On the other hand, the role of chemotherapy in the treatment of these tumors remains undefined.

Very young children (generally defined as those less than 3 years of age) with brain tumors continue to pose a unique therapeutic challenge. CSI is typically not administered to them because of the devastating neurocognitive sequelae associated with its use. [4–6] This limitation in therapy and the distinct biological characteristics of these tumors are likely reasons why children less than 3 years old with embryonal tumors generally have a poor prognosis despite very aggressive treatment.[9,10] However, for selected subgroups of patients, most notably those with localized, completely resected medulloblastoma, survival has improved. In this article, we review the role chemotherapy has played in the treatment of medulloblastoma and high-grade gliomas.

Older Children with Medulloblastoma

The cure rates for children and young adults diagnosed with medulloblastoma have improved significantly in the past 3 decades (Table 1).[11] Improved ability to perform gross total resections, introduction of magnetic resonance imaging (MRI) to accurately stage patients, advanced techniques to deliver radiation therapy, and improved supportive care have all contributed to this success, but the introduction of chemotherapy has played a key role.

The first randomized study that suggested the efficacy of chemotherapy in medulloblastoma treated all patients with 36 Gy CSI with a boost to posterior fossa of 54 Gy and weekly vincristine during radiation therapy. The patients were subsequently randomized to receive either no adjuvant chemotherapy or 8 cycles of lomustine, prednisone, and vincristine. Among the patients treated with adjuvant therapy, those with more advanced disease had a survival advantage compared with patients on the nonchemotherapy arm.[12] The first International Society of Pediatric Oncology (SIOP) trial with a similar study design demonstrated similar results.[13] Because of the deleterious neurocognitive and neuroendocrine consequences associated with this treatment, the next generation of cooperative group studies tested the efficacy of reduced CSI dose for patients with average-risk disease. Patients with gross total resections and no metastatic disease (M0R0) were categorized as having average-risk disease.

In a randomized study for average-risk medulloblastoma patients that compared standard-dose RT (36 Gy to the craniospinal axis and 54 Gy to the posterior fossa) with reduced-dose RT (23.4 Gy to the craniospinal axis and 54 Gy to the posterior fossa), the mean probability of event-free survival (EFS) at 5 years was 67% ± 7.4% and 52% ± 7.7%, respectively ($P = 0.080$).[14,15]

A subsequent pilot study employed reduced-dose CSI (23.4 Gy) with concurrent weekly vincristine during RT and 8 cycles of adjuvant chemotherapy consisting of lomustine, cisplatin, and vincristine that were administered after the completion of RT. Sixty-five children between the ages of 3 and 10 years with average-risk medulloblastoma were enrolled in the study. The probability of PFS was 86% ± 4% at 3 years and 79% ± 7% at 5 years.[16] These study results suggest that a combination of reduced-dose CSI and effective chemotherapy are comparable to the results achieved using standard-dose CSI alone (5-year EFS probability, 67% ± 7.4%). Companion data from the earlier randomized trial conducted by the Pediatric Oncology Group (POG) and the Children's Cancer Group (CCG) suggested a difference in neurocognitive levels measured more than 3 years after irradiation; the decline in intelligence quotient (IQ) scores was most significant in children younger than 8.5 years, and the full-scale IQ scores of patients

after treatment with 36 Gy CSI (70) were lower than those of patients after treatment with 23.4 Gy (85).[17] Together, the greater toxicity associated with higher-dose CSI and the equivalent disease control achieved using adjuvant chemotherapy and reduced-dose CSI support the use of reduced-dose CSI together with chemotherapy as the new "standard" for therapy in children with medulloblastoma. This approach is now widely accepted as standard in North America.

In the recently concluded POG-CCG trial for average-risk medulloblastoma (A9961) all patients were treated with CSI (23.4 Gy) and with posterior fossa boost (55.8 Gy); vincristine was administered weekly during RT. After the completion of RT, patients were randomly assigned to groups that received either the standard regimen of lomustine, cisplatin, and vincristine or the alternative regimen of cyclophosphamide, cisplatin, and vincristine. The 5-year EFS for the 379 eligible patients enrolled in the study was 81 ± 2% and there was no difference in EFS in either arm of the study.[3] On the basis of this result, the current Children's Oncology Group is conducting a randomized study that is seeking to further reduce the dose of CSI to 18 Gy while maintaining the same degree of disease control.

Recently concluded studies from Europe have attempted to answer the question of timing of chemotherapy in relation to RT. The SIOP II study clearly demonstrated that use of prolonged pre-RT chemotherapy negatively affects the EFS estimate for average-risk patients. The negative result could also be attributed to the choice of drugs given before RT, because this chemotherapy regimen did not contain cisplatin, a drug that is particularly effective against medulloblastoma.[18] The recently concluded SIOP III study compared EFS estimates for patients treated with RT alone with those for patients treated with vincristine, carboplatin, cyclophosphamide, and etoposide for 4 cycles and subsequent RT. The dose of CSI was 36 Gy, and the dose to the posterior fossa was 56 Gy. In contrast to US studies that exclude M1 patients from average-risk protocols, patients with M0 and M1 disease were enrolled on this study; therefore the comparison of these data with those from the US is difficult. Of the 217 patients enrolled in the SIOP III study, 179 were eligible for analysis. The EFS probability at 5 years for the group that received chemotherapy and RT was 74%, whereas that for the group that received only RT was 60% ($P = 0.036$). This study confirms that postoperative standard-dose CSI alone achieves 5-year EFS rates of between 60% to 65% and that this can be improved with the addition of platinum-based chemotherapy.[19]

The HIT '91 trial compared the outcome of patients receiving pre- or post-RT chemotherapy. Two hundred eighty patients were enrolled in the study. Patients with M1 disease and residual tumor following surgery were included in the average-risk group. Included among the 234 average-risk patients were 69 patients with residual tumor and 49 patients with M1 disease. Once again, these disease risk criteria render any comparisons with US study data problematic. Post-RT chemotherapy included 8 cycles consisting of lomustine, cisplatin, and vincristine. RT for all patients consisted of CSI (35.2 Gy) and irradiation of the posterior fossa (55.2 Gy). Pre-RT chemotherapy included procarbazine, ifosfamide/etoposide, high-dose methotrexate, cisplatin, and cytosine arabinoside (ara-C). Patients whose tumor responded poorly to the pre-RT chemotherapy were given additional chemotherapy consisting of carboplatin, lomustine, and vincristine after RT. The 5-year PFS estimate for patients in the post-RT chemotherapy arm was 78% ± 6%, whereas that for patients in the pre-RT chemotherapy group was 65% ± 5% ($P = .03$).[20] The results for the post-RT chemotherapy arm confirm those seen in US studies in which a similar approach was used, albeit with a lower dose of CSI and a more clearly defined group of average-risk patients.

Collectively these studies have demonstrated that the addition of adjuvant chemotherapy has improved the cure rates for average-risk medulloblastoma. Current protocols are testing the feasibility of further reduction in the dose of CSI.

Chemotherapy for high-risk patients

Attempts to improve survival estimates for high-risk patient (≥ 1.5 cm^2 residual disease or presence of metastatic disease) have relied on a variety of chemotherapy regimens administered before or after RT (Table 1). Historically, high-risk patients treated with RT alone have had 5-year PFS estimates of 25% to 40%.[21] In a trial conducted at 5 institutions and reported by Packer et al, the 5-year PFS probability was 67% ± 15% for 15 patients with M+ disease treated with RT with concurrent vincristine and adjuvant chemotherapy consisting of lomustine, cisplatin, and vincristine.[22] The effectiveness of combined modality therapy on the PFS probability of high-risk patients has been confirmed in a recently reported POG study (POG 9031). Of the 224 patients enrolled in the study, 94 patients had M+ disease. Patients were randomly assigned to two groups that received 3 cycles of cisplatin and etoposide either before or immediately after RT; all patients subsequently received 8 cycles of cyclophosphamide and vincristine. Patients with M1 disease received 35.2 Gy CSI, and most patients with M2/M3 disease received 40 Gy CSI with a boost of 4.8 Gy to gross sites of metastatic disease. The dose of irradiation to the posterior fossa ranged from 53.2 to 54.4 Gy. The 5-year EFS estimate for the patients with M+ disease was approximately 55%, a result that confirms the pilot experience of Packer et al.[23]

The CCG 921 study, another large randomized study that incorporated pre-RT and post-RT arms, 203 patients with high-risk medulloblastoma. Of these, 188 patients were randomly assigned to one of 2 treatment groups: an experimental arm, which received 2 cycles of “8-in-1” chemotherapy pre-RT and then an additional 6 cycles of the same chemotherapy, or a standard arm, which received chemotherapy similar to the regimen in the study by Packer and colleagues described above. Patients received 36 Gy CSI with a further RT boost to the primary tumor site. Estimated 5-year PFS for the entire cohort of patients was 54% ± 5%. Patients treated with the standard regimen of lomustine, vincristine, and prednisone had a 5-year PFS probability of 63% ± 5%. This estimate is similar to those noted from the Packer study and the POG study and superior to those achieved with the investigational 8-in-1 regimen.[24]

For high-risk patients, the use of pre-RT chemotherapy for a prolonged period of time yielded results that were clearly inferior to those obtained by the use of a shorter window (approximately 6 weeks to 8 weeks of chemotherapy). Results from the PNET III trial and the HIT 91 trial that used pre-radiation chemotherapy did not demonstrate a survival advantage for patients despite the use of drugs that were active against medulloblastoma. The EFS for M2–M3 patients were 34.7% (n = 68) at 5 years and 30% (n = 19) at 3 years for the PNET III and HIT trials, respectively.[20, 25]

The best result for high-risk medulloblastoma to date has been published by a consortium of investigators led by St. Jude Children’s Research Hospital. Following maximal surgical resection of the tumor, therapy consisted of CSI (36 Gy M0–M1; 39.6 Gy M2–M3) with an additional RT boost to the primary tumor bed and a 2-cm margin delivered by 3-dimensional conformal technique. Six weeks after completion of RT, these investigators used 4 courses of cyclophosphamide-based dose-intensive chemotherapy, with hematopoietic stem cell support, over 16 weeks. The 5-year EFS for 48 patients with high–risk medulloblastoma was 70% at 5 years.[2] This study suggests that chemotherapy does significantly improve the survival for patients with high-risk medulloblastoma but the sequencing of chemotherapy is crucial to achieve good results. Despite using drugs with proven efficacy against medulloblastoma, neoadjuvant chemotherapy used for a duration of greater than 6 weeks may have a detrimental impact on EFS in high-risk patients.

Genomewide analysis using microarray technology has contributed significantly to our understanding of medulloblastoma biology.[26,27] It is now apparent that medulloblastoma is not a single disease entity but actually consists of tumors that arise due to distinct underlying

molecular aberrations and that have different pathological morphology that affect prognosis.[28] Future trials will seek to leverage this knowledge to design molecular and clinical risk-adapted trials that combine standard chemotherapy drugs and more novel molecularly targeted therapies.[29,30]

High -Grade Gliomas

This histologically diverse group of tumors consists of anaplastic astrocytoma (AA) (World Health Organization [WHO] grade III), glioblastoma multiforme (GBM) (WHO grade IV) and, less commonly, high-grade oligodendroglial or mixed astrocytic tumors (WHO grade III). High-grade gliomas comprise approximately 8% to 12% of all childhood CNS tumors and most often originate from the supratentorial area, but rarely they can also originate from the cerebellum. Their incidence in childhood peaks among older adolescents; however, they do occur rarely in young children. In spite of modern aggressive multimodality therapy including surgery, RT, and chemotherapy, survival remains dismal.[8] Outcome is worse for children with glioblastoma than for those with anaplastic astrocytoma.[31] The best outcomes are obtained for children with high-grade oligodendroglial or mixed astrocytic tumors.[31] Maximum safe surgical resection and RT form the backbone of therapy for pediatric high-grade glioma. In contrast, the role of chemotherapy for the treatment of these neoplasms remains undefined. Despite decades of intensive investigation, no single chemotherapeutic regimen stands out as particularly beneficial and no standard chemotherapy is available for children with high-grade glioma. [8]

The CCG 943 trial, after initial surgery, randomized patients with high-grade astrocytoma to receive local RT alone or RT with weekly vincristine, followed by 1 year of prednisone, lomustine, and vincristine (PCV).[32] A total of 58 patients were enrolled in this study (40 patients with GBM and 18 with AA). Patients treated with RT alone had a 5-year PFS rate of 18% compared with 46% for those who received RT and chemotherapy. Notably, this study demonstrated a statistically significant improved outcome for patients with GBM treated with chemotherapy: estimated 5-year PFS was 42% compared with 6% for those treated with RT alone. However, these results have never been reproduced in other studies, raising concerns about the histologic diagnosis of these patients.

The subsequent CCG study, CCG 945, compared RT and PCV chemotherapy (CCG 943 therapy – standard arm) to a combination of local RT and 8-in-1 chemotherapy administered pre-and post-RT.[31] The study enrolled 172 newly diagnosed children with high-grade glioma who had undergone surgical resection. There was no statistical difference in 5-year PFS between patients receiving standard therapy and the group receiving the 8-in-1 regimen (26% compared with 33% ($P > .52$)). The 5-year PFS rate was 28% ± 7% for patients with AA and 16% ± 7% for patients with GBM, respectively. A follow-up retrospective analysis by a panel of expert neuropathologist of 169 of 172 tumor samples in the above study revealed that 30% of the patients enrolled in this study did not harbor high-grade gliomas. When tumors were classified according to institutional and consensus panel criteria, the 5-year survival estimates dropped from 36% ± 5% (standard) and 40% ± 5% (“8 in 1”) to 19% ± 5% (standard) and 23% ± 5% (“8 in 1”), demonstrating the importance of central pathologic review.[33]

German investigators, on the other hand, tested the efficacy of alternative cytotoxic agents applied pre-RT, termed sandwich chemotherapy. Patients were randomly assigned after surgery to receive alternating cycles of ifosfamide/etoposide, high-dose methotrexate and cisplatin/cytarabine for 17 weeks, followed by RT or RT along with vincristine followed by 8 cycles of vincristine, lomustine, and cisplatin.[34] Poor patient accrual resulted in early closure of the study and the study randomized a total of 52 children with non-brainstem high-grade glioma. Although the EFS in both groups were similar, patients receiving sandwich

chemotherapy who underwent more radical resections had a statistically better survival compared with a similar group receiving maintenance chemotherapy.[34] For adults with newly diagnosed GBM, temozolomide is considered the standard chemotherapy.[35] The standard of care for adult patients with GBM consists of radiation therapy followed by 6 months of temozolamide.[36] The DNA repair gene, O^6-methylguanine-DNA-methyltransferase (*MGMT*), removes methylated adducts from the O^6-guanine position, which represents the principal mechanism of resistance to temozolomide. In adults, epigenetic silencing of the *MGMT* gene by promoter methylation has been associated with improved outcome for patients with GBM receiving temozolomide.[36,37] However, whether such a correlation exists for children with high-grade glioma remains to be determined.

A multi-institutional study coordinated by St. Jude Children's Research Hospital (SJHG98) between 1999 and 2002 tested the efficacy of temozolomide in patients with non-brainstem high-grade glioma (48% GBM, 32% AA). Following surgery, patients received RT and 6 cycles of temozolomide. [38] The study also included an optional window therapy of irinotecan. A total of 31 eligible patients were enrolled. The 1- and 2-year PFS estimate in this study were 43% ± 9% and 11% ± 5%, respectively. The 1- and 2-year overall survival (OS) estimates were 63% ± 8% and 21% ± 7%, respectively.[38] Patients withAA fared significantly better than those with GBM; 2-year PFS estimate was 0 for 15 patients with GBM compared with 20% ± 10% for patients with AA. The median time to progression after the start of RT was 0.8 years (range, 0.2 to 1.9 years).[38] The marked differences in response to temozolomide between adults and children with high-grade glioma highlight the distinct underlying biology between these groups and supports the development of therapeutic strategies based on tumor biology rather than similarities in histologic appearance.

An extensive body of knowledge regarding genetic and molecular abnormalities found in adult high-grade gliomas now exists.[39] In contrast, information about alterations present in pediatric high-grade glioma is more limited. This knowledge, coupled with a failure of current treatments, has led to the development of a variety of novel therapies that have more specific activity against tumor cells than standard cytotoxic agents.[40] The most promising of these agents for high-grade gliomas include molecularly targeted agents such as the small molecule tyrosine kinase inhibitors[41] and treatments directed against the tumor vasculature, known as antiangiogenic agents.[42] These advances hold great promise to improve future therapy.

Encouraging results have recently been reported from an adult phase 2 trial for patients with recurrent high-grade glioma using the antiangiogenic agent bevacizumab (Avastin), a humanized immunoglobulin monoclonal antibody that binds to and inhibits activity of vascular endothelial growth factor (VEGF) in combination with irinotecan (CPT11), [43] a topoisomerase I inhibitor. In the study reported by Vredenburgh and colleagues,[43] 6-month PFS and OS were 46% (95% CI, 32% to 66%) and 77% (95% CI, 64% to 92%) respectively, which compares favorably with historical controls. The median PFS of 35 GBM patients was 24 weeks (95% CI, 18 to 36 weeks) and OS was 42 weeks (95% CI, 35 to 60 weeks) respectively. Twenty of 35 patients had at least a partial response. Seven have completed a full year of therapy and 6 of the 7 had a cold PET scan, suggesting no residual high-grade tumor.[43] The Pediatric Brain Tumor consortium (PBTC) is conducting a phase 2 trial (PBTC-022) using a combination of bevacizumab plus irinotecan in children with recurrent, progressive, or refractory malignant gliomas and diffuse/intrinsic brainstem gliomas to determine if the adult data can be replicated in pediatric patients.

Diffuse Pontine Glioma

The vast majority of pontine gliomas (85% to 90%) are diffuse infiltrative, malignant (AA/GBM) intrinsictumors that are not amenable to resection. The diagnosis is based on typical

MRI appearance and a biopsy is not indicated. Despite numerous trials, survival has not changed for decades; the mediansurvival after diagnosis remains less than 1 year and long-term OS is still less than 10%.[44] RTforms thecornerstone of treatment but is not curative. RT produces responses in many patients, but for the vast majority tumor progression usually occurs within 5 months to 10 months from the beginning of RT. No chemotherapeutic agent or regimen,[44] including myeloablative regimens with autologous stem cell rescue (ASCR), [45] have influenced survival. Multi-institutionaltrials using high-dose hyperfractionated X-ray therapy have also failed to prolongsurvival.[46] These dismal outcomes have prompted investigators to trial various molecularly targeted and/or antiangiogenic therapies in combination with RT.

Brain Tumors in Very Young Children

The realization in the 1980s that CSI results in devastating consequences on the developing CNS of very young children prompted investigators to devise strategies to avoid or delay CSI for this group of children. During the 1990s, several studies were conducted to address this issue (Table 2). The POG and CCG adopted a delayed radiotherapy approach (POG 8633/34 [termed Baby POG-1][47,48] and CCG 921 trials[49]). In Baby POG-1, children under the age of 3 years were treated with chemotherapy consisting of vincristine, cyclophosphamide, etoposide, and cisplatin. Depending on patient age, CSI was delivered at 1 or 2 years post-diagnosis. Using this approach CSI was successfully delayed in only 40% of patients. The 5-year PFS and OS for all medulloblastoma patients were 31.8 ± 8.3% and 39.7 ± 6.9% respectively. Of note, medulloblastoma patients with nonmetastatic and gross totally resected tumor (M0R0) had much better outcomes, with 5-year OS of 69%. In an attempt to improve outcome, the succeeding POG study 9233/34 (termed Baby POG-2) [50] intensified the chemotherapy regimen. Patients were randomized between standard Baby POG-1 treatment or an intensified version of Baby POG-1 therapy in which the same drugs were administered at higher doses and more frequently. No difference in EFS or OS was observed between patients receiving standard or intensified Baby POG therapy.[50]

The CCG, which also adopted the strategy of delayed CSI in infants with brain tumors, conducted the CCG 921 trial[49] over the same time period as the Baby POG-1 study. However, this study only included children younger than 18 months of age. Patients were treated with the 8-in-1 chemotherapy regimen, followed by delayed CSI or focal RT. Only 10% (9 of 91) of patients received the planned RT. Patients with medulloblastoma had a 3-year PFS of 22%. The outcome for patients with M0R0 disease was marginally superior (5-year PFS. 30%).[49] Similar to the POG study, the succeeding CCG trial (CCG 9921) also used a strategy of more intensive chemotherapy to improve outcome. Children younger than 3 years of age were randomly assigned to receive 1 of 2 5-cycle induction chemotherapy regimens, followed by a uniform regimen of maintenance chemotherapy for 56 weeks. Patients with residual or metastatic disease were to receive focal RT or CSI at the end of maintenance or at 3 years of age, whichever came sooner. However, like the previous CCG trial, only a minority (40%) of patients received RT as planned. There was no difference in EFS or OS between chemotherapy arms. Although outcomes were improved compared with the previous CCG trial, they were comparable to the Baby POG-1 results, with a 5-year EFS for all medulloblastoma patients of 32 ± 5% and 5-year OS for completely resected M0 medulloblastoma of 54 ± 8%.[51] These studies demonstrated that RT could be delayed or even omitted without compromising survival in a subset of medulloblastoma patients younger than 3 years of age at diagnosis.

The less than optimal survival and neurocognitive results achieved using delayed CSI prompted investigators to evaluate alternative approaches.[10] One alternative to delayed CSI is to only administer RT at the time of disease recurrence or progression. The French BBSFOP trial adopted such a strategy by treating patients younger than 4 years of age with only conventional

chemotherapy, reserving RT (focal to the posterior fossa only) and combined high-dose chemotherapy with ASCR, for patients with tumor progression or recurrence.[52] The BBSFOP chemotherapy regimen resulted in a 5-year PFS of 29% (95% CI, 18% to 44%) for M0R0 patients, revealing that this subset can achieve long-term survival with no RT and relatively mild chemotherapy. Many patients were successfully salvaged with RT (either CSI or focal RT, depending on the extent of disease) and high-dose chemotherapy with ASCR, resulting in a 5-year OS for M0R0 patients of 73% (95% CI, 59% to 84%).[52]

To avoid CSI, German investigators used a strategy of high-dose systemic and intensive intraventricular methotrexate combined with standard chemotherapy.[53] Using this approach, the HITSKK92 trial achieved the best results to date for children less than 3 years old with M0/M1R0 medulloblastoma (n=17), with 5-year PFS of 82 ± 9% and OS of 93 ± 6%. Outcomes for patients with residual disease (n=14) were also somewhat better than in prior series, with 5-year PFS of 50 ± 13% and OS of 56 ± 14%. Only patients with macroscopic metastasis (M2-M3) (n=12) fared poorly, with 5-year PFS of 33 ± 14% and OS of 38±15%. This study reported no toxic deaths, but there was a very high frequency (19 of 23 [83%] evaluated patients) of asymptomatic leukoencephalopathy noted on MRI, most likely attributable to the intensive use of intrathecal methotrexate. Additionally, the mean IQ of survivors, although higher than historical controls that received whole brain RT, was significantly lower than that of age-matched controls.[53] This study revealed that the majority of young children without macroscopic metastasis and completely resected medulloblastoma can be cured with chemotherapy alone, but at a cost of methotrexate-induced neurotoxicity.

The use of myeloablative chemotherapy with ASCR has also been investigated as an alternative to CSI. This approach was used by the Head Start II trial, which used 5 cycles of induction chemotherapy very similar to regimen A of CCG 9921, but with the addition of high-dose intravenous methotrexate, followed by a single consolidation course of myeloablative therapy using carboplatin, thiotepa, and etoposide with ASCR. Using this strategy, the Head Start II trial has achieved the best results to date for young children (defined as age less than 6 years in this trial) with metastatic medulloblastoma (M1–M3) (n=21), with 3-year EFS of 49% (95% CI, 27% to 72%) and OS of 60% (95% CI, 36% to 84%), respectively.[54] Though promising, interpretation of these results is limited by the small size of the study and inclusion of older children (only 9 patients under age 3 years at diagnosis were enrolled).[54] Children less than 3 years of age with M0 medulloblastoma treated on Head Start I and II trials were treated with identical therapy as patients with metastatic disease, except they did not receive high-dose methotrexate. For patients with M0R0 medulloblastoma (n=14) the results of this trial are comparable with those of the German group, with 5-year EFS of 64 ± 13% and OS of 79 ± 11%.[55] However, these results were achieved with a high toxic death rate (19%) from treatment related complications.[55] This strategy appears to add no benefit for patients with nonmetastatic residual disease (M0R1) (n=7), since the 5-year EFS of 29 ± 17% for this group[55] is comparable to the CCG 9921 trial result of 26 ± 9%,[51] which was achieved without the use of myeloablative chemotherapy with ASCR.

On the basis of the Head Start regimen, the CCG tested the feasibility of delivering multiple courses of myeloablative chemotherapy with ASCR (termed tandem transplants) as part of the CCG 99703 trial (n=21). Patients younger than 3 years of age received 3 cycles of intensive standard chemotherapy followed by 3 cycles of myeloablative chemotherapy with ASCR. Results are pending.

Recent improvements in radiotherapy delivery techniques, permitting more precise tumor targeting, have generated renewed interest in the use of focal RT for very young patients with localized disease. This strategy has been implemented in 2 recent trials: the COG P9934 study and the PBTC-001 study. The COG P9934 included focal RT after 16 weeks of induction

chemotherapy for patients with M0R0 medulloblastoma. In the PBTC-001 study, patients received standard chemotherapy plus intrathecal mafosfamide for 20 weeks, followed by focal RT and then 20 weeks of maintenance chemotherapy. Results from these trials are pending.

Atypical teratoid/rhabdoid tumor (ATRT) has only recently been recognized as a distinct tumor entity from other CNS embryonal tumors.[56,57] ATRT is a highly aggressive tumor that occurs primarily in children younger than 2 years of age and frequently presents with metastatic disease at diagnosis. In the past, many patients with ATRT were probably classified with medulloblastoma or PNET. Thus, the classification of ATRT as a distinct entity may also account for some of the improvement in outcome for young children with medulloblastoma and primitive neuroectodermal tumors (PNET). ATRT is characterized by alterations in the *SMARCB1* (also known as *INI1/hSNF5*/) gene on chromosome 22q11. The majority (85%) of ATRTs have inactivation of the *SMARCB1* gene, either through homozygous deletions or loss of one allele with concomitant mutation of the other copy. Older children with ATRT have been successfully treated with a combination of complete resection, CSI, and high-dose chemotherapy with ASCR.[58] In contrast, possibly because of the omission of CSI, outcomes for children younger than 3 years of age are dismal.[51,58] The 2-year EFS for 28 children less than 3 years old treated on the CCG 9921 trial was 14 ± 7%. [51] Likewise, in the St. Jude experience reported by Tekautz and colleagues, the 2-year EFS for the 22 children less than 3 years of age at diagnosis was 11 ± 6%. [58] Effective chemotherapy regimes for young children with ATRT remain elusive.

Conclusions

While surgery and radiotherapy are the mainstay of therapy for older children with medulloblastoma, chemotherapy has also played a key role. Medulloblastoma is the first brain tumor to show efficacy of chemotherapy in large prospective trials. On the other hand, many children with brain tumors remain incurable with current therapies. Effective chemotherapy regimens remain elusive for almost all patients with high-grade cortical or brainstem gliomas and for most young patients with residual or metastatic disease of any histology. In the past 3 decades, chemotherapeutic agents have been extensively evaluated for the treatment of brain tumors in a myriad of schedules, doses, and combinations. A plateau in efficacy has been reached. Further treatment intensification using conventional nonspecific chemotherapy is more likely to result in additional toxicity without major advances in survival. Modest improvements in outcome may be achieved by further refining treatment schedules, introducing new chemotherapeutic agents.

Novel approaches to chemotherapy administration and delivery such as continuous low-dose administration of chemotherapy, known as metronomic chemotherapy, has been shown to have antiangiogenic properties and demonstrated objective response rates in pediatric patients.[59] Additionally, convection-enhanced delivery of immunotoxin conjugates is being explored as potential therapy for pediatric cortical high-grade gliomas.

Although conventional chemotherapeutic agents continue to be developed to reduce toxicity and/or improve efficacy, the remarkable advances made in knowledge of tumor biology in the past decade have shifted the focus onto novel agents that target molecular changes crucial for tumor proliferation or survival. These selective agents are predicted to be less toxic to normal cells and it is anticipated that they will be more effective than currently used nonspecific chemotherapeutic agents. The toxicity and efficacy of several of these novel agents is currently being assessed in children with brain tumors. Ultimately, if these novel therapies prove effective, their role in combination with established chemotherapeutic agents will need to be assessed.

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Table 1

Prospective Clinical Trial Results for Older Children with Average-Risk and High-Risk Medulloblastoma

Trial	n	Treatment	Radiotherapy dose		5-y EFS (± SE)*	Ref
			CSI	PF		
Average risk (M0R0)						
CCG 9892 (1990–1994)	65	Reduced-dose RT with weekly VCR followed by CHT (VCR, CDDP, & CCNU)	23.4 Gy 55.8 Gy		78 ± 5%	16
SIOP-PNET3 (1992–2000)	179	Standard-dose RT only vs. pre-RT CHT (VCR, VP-16, CBDA, & Cyclo)	35 Gy	55 Gy	60% vs. 74% *P* = .036	19
HIT-91 (1991–1997)	118	Pre-RT CHT (ifos, ara-C, VP-16, HD-MTX, CDDP) vs. Post-RT CHT (VCR, CDDP, & CCNU)	35.2 Gy 55.2 Gy		65 ± 5% vs. 78 ± 6% (3-y EFS) *P* = .03	20
A9961 (1996–2000)	383	Weekly VCR during RT, then CCNU, CDDP, VCR vs. cyclo, CDDP, VCR	23.4 Gy	55.8 Gy	82 ± 3% vs. 80 ± 3%	3
SJMB96 (1996–2003)	86	Reduced-dose RT followed by 4 cycles of high-dose CHT with ASCR (VCR, CDDP, & cyclo)	23.4 Gy	55.8 Gy	83% (95% CI, 73–93)	2
High risk (M1–M3 ± R1)						
HIT-91 (M2–M3) (1991–1997)	19	As above (separate results for the 2 treatment arms were not provided)	35.2 Gy	55.2 Gy	30 ± 15% (3-y EFS)	20
SIOP-PNET3 (M2–M3) (1992–2000)	68	Pre-RT CHT (VP-16 VCR, cyclo, & CBDA)	35 Gy	55 Gy	34.7%	25
CHOP (M1–M3)	15	Weekly VCR during RT, then CCNU, CDDP, VCR	36 Gy	55.8 Gy	67 ± 15%	22
SJMB96 (M1–M3) (1996–2003)	48	Topotecan window pre-RT followed by 4 cycles of high-dose CHT with ASCR (VCR, CDDP, & cyclo)	36–39.6 Gy	55.8 Gy	70% (95% CI, 55–85)	2

Abbreviations: ara-C, cytosine arabinoside; ASCR, autologous stem cell rescue; CBDA, carboplatinum; CCNU, lomustine; CDDP, cisplatin; CHT, chemotherapy; CSI, craniospinal irradiation; Cyclo, cyclophosphamide; EFS, event-free survival; ifos, ifosphamide; HD-MTX, high dose methotrexate; PF, posterior fossa; RD, residual disease; ref, reference; RT, radiation therapy; VCR, vincristine; VP-16, etoposide; 8-in-1, 8 chemotherapeutic agents administered in one day (consisting of VCR, methylprednisolone, CCNU, CDDP, hydroxyurea, procarbazine, ara-c, and cyclo).

*Unless otherwise stated.

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Table 2

Results of Prospective Clinical Trials for Infants and young children with Medulloblastoma

Trial	n	5-y Event-Free Survival (% ± SE)*	5-y Overall Survival (% ± SE)*	Reference
M0R0				
Baby POG	13		69	47, 48
CCG 9921	38	41 ± 8	54 ± 8	51
SFOP	47	29 (95% CI, 18–44)	73 (95% CI, 59–84)	52
HIT-SKK92	17	82 ± 9	93 ± 6	53
Head Start I+II (age < 3 y)	14	64 ± 13	86 ± 9	55
M0R1				
CCG 9921	23	26 ± 9	40 ± 11	51
SFOP	17	6 (95% CI, 1–27)	41 (95% CI, 22–64)	52
HIT-SKK92	14	50 ± 13	56 ± 14	53
Head Start I+II (age < 3y)	7	29 ± 17	57 ± 19	55
Metastatic (M+)				
CCG 9921	31	25±8	31 ± 9	51
SFOP	15	13 (95%CI, 4–38)	13 (95% CI, 4–38)	52
HIT-SKK92	12	33 ± 14	38 ± 15	53
Head Start II (age < 6 y)	21	3-y EFS 49 (95% CI, 27–72)	3-y OS 60 (95% CI, 36–84)	54

Abbreviations: CI, confidence interval; SE, standard error.