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New Chemotherapy Strategies and Biological Agents in the Treatment of Childhood Ependymoma

Karen D. Wright[1,2,3] and **Amar Gajjar**[1,2]

[1]Division of Neuro Oncology, St Jude Children's Research Hospital, 262 Danny Thomas Place, Mailstop 260, Memphis, TN 38105

[2]Department of Oncology, St Jude Children's Research Hospital, 262 Danny Thomas Place, Mailstop 260, Memphis, TN 38105

[3]Department of Developmental Neurobiology, St Jude Children's Research Hospital, 262 Danny Thomas Place, Mailstop 260, Memphis, TN 38105

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Introduction

As the third most frequent brain tumor in children, ependymomas comprise approximately 9% of primary CNS tumors in patients less than 18 years of age and remain difficult to treat due to the high frequency of chemotherapy and radiation resistance [1]. The mean age at diagnosis ranges from 51–71 months [2–5] and 25–40% are diagnosed in children less than 3 years of age [6]. Children tend to have a worse outcome than adults; 40–60% of children will die of their disease, further highlighting the need for novel treatment strategies [1,7,8]. Recurrences, which are not uncommon, typically occur locally with a median time to recurrence of 13–25 months; 20% of failures have an isolated distant recurrence [2–4,8–10]. Dissemination at the time of diagnosis is generally a rare event in patients with ependymoma, and at present, prognosis remains relatively poor for those patients despite multimodality treatment strategies [11].

Treatment Standards

The standard of care for ependymoma remains surgical resection followed by post-operative radiation therapy (RT) directed at the primary site, resulting in a 5 year progression-free survival (PFS) ranging from 50–60% [4,9,12–14]. For very young children (age < 3 years), immediate post-op irradiation is not widely accepted due to the associated neurocognitive sequelae, and multi-agent chemotherapy has been given in an effort to delay or avoid irradiation. In addition, there is no consensus in regard to "standard of care" for those patients with metastatic disease at the time of diagnosis.

To date, there has been no convincing role for chemotherapy in the treatment of ependymoma using conventional agents. In single agent phase II trials, only cisplatin has been reported to be particularly active in ependymoma with a response rate of 30% (15–17). Carboplatin [18,

Corresponding Author: Karen Wright MD, Department of Oncology, St Jude Children's Research Hospital, 262 Danny Thomas Place, Mailstop 260, Memphis TN 38105, karen.wright@stjude.org, phone: 901-595-2615, fax: 901-521-9005.

19], ifosfamide [20] and etoposide [21,22] have demonstrated only modest activity. In addition, temozolomide, a prodrug with little, if any, pharmacologic activity until it is hydrolyzed to the active alkylating metabolite, has proved disappointing in ependymoma. No responses were observed in patients enrolled on the recent phase II study of temozolomide in children and adolescents with ependymoma under the direction of the Children's Oncology Group [23].

Generally the results of trials using adjuvant combination chemotherapy post-irradiation in patients with newly diagnosed ependymoma have not shown improvement in survival rates compared to those patients treated with radiation therapy alone. A study conducted by St. Jude Children's Research Hospital evaluated the use of conformal radiation only to the postoperative tumor bed in 88 children with ependymoma including 48 children under age 3 at the time of RT. Notably 3 year PFS was approximately 75% without the use of chemotherapy [14].

Role of Chemotherapy in Infants and Young Children with Ependymoma

The results of major clinical trials evaluating the role of chemotherapy conducted among infants and young children with ependymoma are summarized in Table 1. In a study by the Children's Cancer Group (CCG 921), children over 2 years of age with newly diagnosed ependymomas were treated with CSI and randomized to receive adjuvant chemotherapy with either CCNU, vincristine and prednisone or the "8 in 1" regimen [8,12]. No difference in survival was noted between the two regimens, and therefore no advantage gained in using chemotherapy compared to historical controls. Similarly, Timmerman et al. [24] reported no benefit to the use of adjuvant chemotherapy in 55 patients with newly diagnosed anaplastic ependymoma treated on the HIT 88/89 and 91 trials with chemotherapy before (n=40) or after irradiation (n=15).

The best response rates to combination chemotherapy in primary ependymoma have been demonstrated in younger children who received pre-irradiation chemotherapy in an attempt to delay RT. In the POG 8633 infant study for patients less than 3 years of age, Duffner et al. reported a 48% response rate following two cycles of combination chemotherapy that consisted of vincristine, cyclophosphamide, cisplatin and etoposide in 25 children with residual tumor after initial surgery, demonstrating that the use of post-operative chemotherapy may allow the delay of RT for a clinically relevant period of time in younger children with ependymoma [25]. Similarly, in a recent study by the French Society of Pediatric Oncology (SFOP), children with ependymoma under the age of 5 were treated with 7 cycles of alternating courses of procarbazine and carboplatin, etoposide and cisplatin, vincristine and cyclophosphamide over 1.5 years [26]. Despite the lack of any partial (PR) or complete responses (CR) in patients with residual disease post-initial surgery, 23% of patients remained alive at 4 years without the use of RT, suggesting that there exists a small subset of patients for whom cure may be possible with surgery and post-operative chemotherapy alone.

A number of other studies have revealed mixed results. White et al. found an 86% response rate to 4 cycles of vincristine, etoposide and cytoxan in 7 children < 4 years of age with newly diagnosed ependymoma [27]. The CCG 9921 trial utilized delayed RT achieving similar results to POG 8633 with a 5 year OS of 67% for patients with completely resected M0 disease; however, 5 year PFS for this group was only about 33% [12]. Among 25 children ages 2 weeks to 15 years enrolled on study at MD Anderson Cancer Center, 5 patients were less than 3 years of age and the five year PFS 40% [28]. The Head Start I/II trial, which used five cycles of induction chemotherapy, including IV methotrexate followed by a consolation regimen of myeloablative chemotherapy with autologous stem cell rescue, did not improve outcome for patients with ependymoma [29].

Role of Chemotherapy in Older Children with Ependymoma

Few phase III studies have demonstrated any benefit from adjuvant chemotherapy among older children (see Table 2) [5,6,30,32–34]. The CCG 9942 study for patients age 3–21 years of age with histologically proven intracranial ependymoma and evidence of residual tumor on postoperative imaging were nonrandomly assigned to receive pre-irradiation chemotherapy consisting of vincristine, cisplatin, etoposide and cyclophosphamide [30]. Needle and colleagues also reported encouraging results in 19 patients between 3 and 14 years of age treated with post-operative RT and chemotherapy consisting of carboplatin and vincristine alternating with ifosfamide and etoposide for a total of 4 cycles [31]. The 5-year actuarial progression free survival (PFS) of 74% for patients with post-operative residual ependymoma was higher than previously reported for RT alone, suggesting a possible role for multi-alkylator chemotherapy in incompletely resected ependymoma; however, this data has not been confirmed in a large prospective randomized trial. By comparison, Shu and colleagues retrospectively reviewed a cohort of 49 patients with ependymoma, which included the cohort from Needle's work. Those patients underwent surgery, radiation and a variety of chemotherapeutic regimens with 5 year OS and PFS rates of 66.2 and 40.7%, respectively (32). In contrast, the CCG 942 study, which included children up to 16 years of age, did not show improved outcomes among older patients treated with postoperative craniospinal radiation and then randomized to receive adjuvant chemotherapy consisting of lomustine (CCNU), vincristine and prednisone for one year or observation [6]. The failure free survival and overall survival for the entire group at 10 years was 36 and 39%, respectively, suggesting no improvement in outcome with the use of adjuvant chemotherapy.

Various studies among older children have focused primarily on outcomes following extent of tumor resection at surgery. Among 35 children up to the age of 16 years with infratentorial ependymoma at Toronto's Hospital for Sick children, OS was 87% (n=9) for patients with gross total resection (GTR) compared to only 30% in those patients undergoing subtotal resection (STR) [33]. Similarly, at the Children's Hospital of Philadelphia (CHOP), 5 year PFS among patients up to the age of 20 years with intracranial ependymoma was 36% overall, but 60% for patients with GTR (n=23) versus 21% with STR or biopsy [5]. Similarly, for those children involved in the MD Anderson Cancer Center trial, 5 year progression free survival was 61% and 37% in those who had complete resection of their tumor versus those with incomplete resection, respectively [34]. Collectively these data conclusively demonstrate that obtaining gross total resection is an important factor in achieving long term disease control.

Role of Chemotherapy in Tumor Resectability

In contrast, the potential importance of adjuvant chemotherapy in facilitating tumor resectability has been reported by Foreman et al. [35]. Adjuvant chemotherapy used between initial and second surgery in 4 patients with ependymoma was associated with a subsequent complete resection in 3 of the patients who remain free of progressive disease 23–34 months after second look surgery. One additional patient included in the study underwent second look surgery, but did not receive adjuvant chemotherapy. This strategy is being further studied in the current COG trial as no study to date has shown that either intensity of chemotherapy or response to chemotherapy correlates with ease of resection at the time of second surgery. The mechanism by which chemotherapy may make a tumor easier to resect is unknown, but could reflect a combination of cytotoxic and anti-angiogenic effects.

Metronomic Drug Dosing

At present, one of current areas of interest focuses on the use of "metronomic" dosing which relies on frequent administration of drug at low doses. An increasing number of preclinical trials support the use of metronomic dosing in order to inhibit angiogenesis [36–39]. Browder

et al. first demonstrated that administration of cyclophosphamide at both standard maximum tolerated doses (MTD) and frequent low doses induced tumor cell apoptosis in an experimental model [40]; however, the continuous low dose regimen also produced a more prolonged anti-angiogenic effect. Subsequent preclinical and early clinical studies have demonstrated activity of metronomic chemotherapy against various adult and pediatric tumors [41–8].

New Chemotherapy and Biologic Agents

With the limited role of chemotherapy and inherent side effects of radiation on the developing brain, considerable effort has been placed on the identification of the molecular changes underlying the development of ependymoma in hope of discovering novel therapeutic agents. To achieve that goal, a number of new agents possessing more tumor specific activity than standard cytotoxic agents are under development in addition to a variety of non-specific tumor directed agents. Among them are molecularly targeted agents including small molecule tyrosine kinase inhibitors [49] and antiangiogenic agents [50]. The use of these molecularly targeted therapies, however, presents added challenges in the pediatric population, in that the cell signaling pathways dysregulated in tumorigenesis are often those that are crucial for normal development.

Rationale for use of Gefitinib and Erlotinib

The receptor tyrosine kinase family of transmembrane receptors known as ERBB is involved in a number of cell signaling pathways that control various processes ranging from apoptosis to cell proliferation. Abnormalities of ERBB receptors have been noted in a variety of tumor types as well as ependymoma, specifically epidermal growth factor receptor (EGFR or ERBB1), ERBB2 and ERBB4 [51–57]. Preclinical data from a variety of human cell lines and xenografts have revealed G1 cell cycle arrest and apoptosis when subjected to tyrosine kinase inhibitors [58–59]. Synergistic effects have also been observed in preclinical studies when these small molecular inhibitors were combined with RT or chemotherapy in colon, head and neck and non-small cell lung cancers [60]. Thus, targeting ERBB receptors may prove to be an effective novel therapeutic strategy in patients with ependymoma.

With that in mind, Geoerger and colleagues evaluated gefitinib, a tyrosine kinase inhibitor of transmembrane cell surface receptors, including EFGR, found on both normal and cancer cells, for its antitumor activity and potential to radio-sensitize in vivo xenograft models [61,62]. The exact mechanism of gefitinib's antineoplastic action is unknown, but inhibition of the EGFR pathway is thought to prevent tumor cells from escaping the action of DNA damaging agents. In addition, ionizing radiation can activate EGFR tyrosine phosphorylation, leading to proliferation of surviving cancer cells and possible accelerated cellular repopulation after RT [61]. Thus, adjuvant therapy with gefitinib may block this major cytoprotective response following RT [61]. In fact, combined treatment of Geoerger's xenograft models with RT and gefitinib revealed a trend toward improved anti-tumor activity [61].

One of the most advanced agents in clinical development is erlotinib, an orally available small molecule tyrosine kinase inhibitor of ERBB1 and ERBB2 with good CSF penetration and possibly anti-angiogenic activity in ERBB2 expressing tumors based on its down regulation of VEGF expression both in vivo and in vitro [62–64]. Specifically, when orthotopic xenografts of ERBB2-transfected Daoy cells were used as a model for aggressive medulloblastoma, erlotinib treatment depleted the tumor vasculature, destroyed the self renewing tumor cell population and inhibited tumor growth [63]. Clinically, erlotinib has been well tolerated in a several pediatric phase I studies to date [65–67].

Rationale for use of Bevacizumab

As alluded to above, considerable effort has been focused on identifying the mechanism by which tumors induce angiogenesis in order to target them for therapeutic intervention [50, 68–70]. Development of effective anti-angiogenic treatments, however, remains in its early stages due to the inherent complexity of this process [68–73]. To date, the most studied of these agents has been bevacizumab, a humanized monoclonal antibody to VEGF [50]. When orthotopic xenografts of ERBB2-transfected Daoy cells were used as a model for medulloblastoma as mentioned above, treatment with bevacizumab also affected tumor vasculature and inhibited tumor growth (64). Similar studies by Bao and colleagues also demonstrated that bevacizumab inhibited the growth of tumors derived from stem cell like glioma cells that secrete VEGF in a xenograft model (74).

As a single agent therapy in clinical trials, however, bevacizumab has been shown to be effective only in metastatic renal cell carcinoma in terms of progression free survival [75,76]. Combining bevacizumab with cytotoxic chemotherapy, however, has improved its effectiveness in terms of progression free and overall survival as evidenced by a number of Phase III trials [77,78]. In regard to CNS tumors, bevacizumab has been shown to be effective in adult trials for recurrent high grade glioma [79]. While the prior studies of bevacizumab suggest supporting evidence for the possibility of anti-angiogenic therapy, its effectiveness in ependymoma has yet to be documented.

On the Horizon

Other novel agents include receptor tyrosine kinase inhibitors which interfere with signaling pathways involved in tumor angiogenesis. A number of agents in this group are under development, including sunitinib and sorafinib, which have already been approved by the FDA as single agent therapy for renal cell carcinoma [75]. Sunitinib possesses both antitumor and antiangiogenic effects by inhibiting multiple receptor tyrosine kinases including platelet derived growth factors (PDGFRa, PDGFRb), vascular endothelial growth factors (VEGFR 1-3), FMS-like tyrosine kinase-3 (FLT-3), colony stimulating factor type I (CSF-1R) and glia cell line-derived neurotrophic factor receptor (RET). Similarly, sorafenib, another multikinase inhibitor, affects tumor growth and angiogenesis by inhibiting intracellular RAF kinases and cell surface kinase receptors (VEFGR 2-3, PDGFRb, cKIT, FLT-3). Again, none of these agents have been studied extensively in young children.

Despite advances in the diagnosis and etiology of ependymoma, the role of chemotherapy remains uncertain and the development of new treatment strategies presents a challenge for this disease dependent upon surgery and radiation, yet plagued by the associated physical and cognitive disabilities that may follow those interventions, especially in very young children. The development of novel therapies for patients with ependymoma will depend on a more detailed understanding of the molecular basis associated with the pathogenesis of this disease. Additionally, although molecular profiling of ependymoma is in its infancy, identification of distinct stem cell precursors in ependymoma [62] and emerging data in regard to different tumor subtypes [62,80–83] may facilitate the development of individually-tailored therapies based on cell signaling pathways.

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Table 1

Results of Prospective Clinical Trials for Infants and Young Children with Ependymoma

			Event Free Survival		Overall Survival	
Trial	**N**	**Age (mo)**	**1 year**	**5 years (unless otherwise specified)**	**5 years (unless otherwise specified)**	**References**
CCG 8-in-1	15			22 (3)		8
HIT 88/89/91	55			75.6 (3)		24
GTR	28					
STR	27					
Baby POG 8633	48	<36		25	40.5	25
GTR	23				66	
	8	0–24	87	25.7	37.5	
	8	24–36	94	63.3	87.5	
STR	25				25	
SFOP	73			22 (4)	59 (4)	26
GTR					74 (4)	
STR					35 (4)	
VETOPEC	14				36 (3)	27
CCG 9921	74		72	32	59	12
M0 with min residual	42		79	33	67	
	20		75	29	54	
M0, other M1+	12		42	33	40	
MD Anderson	5				40 (>5)	28

			Event Free Survival	Overall Survival	
Trial	**N**	**Age (mo)**	**1 year**	**5 years (unless otherwise specified)**	**5 years (unless otherwise specified)**	**References**
Head Start I/II	29			12	38	29
GTR	18				42	
STR	11				31	

Table 2

Results of Prospective Clinical Trials in Older Children with Ependymoma

Trial	N	5 Year Event Free Survival (unless otherwise specified)	5 Year Overall Survival (unless otherwise specified)	References
CCG 942	36	36 (10)	39 (10)	6
Hospital for Sick Children	35		45	33
GTR	9		87	
STR	26		30	
CHOP	45	36		5
MD Anderson	25	47		34
GTR	5	61		
STR	20	37		
CCG 9942	84		75	30
<5 yr	23	58(3)		
5–9 yr	34	56(3)		
≥10 yr	27	72(3)		
CHOP	49	40.7	66.20	
GTR	30			
M0 & RT > 54Gy		60.6	83.1	32
STR/biopsy	18			
Unknown	1			