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Pilot Study of Systemic and Intrathecal Mafosfamide followed by Conformal Radiation for Infants with Intracranial Central Nervous System Tumors: A Pediatric Brain Tumor Consortium Study (PBTC-001)

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Abstract

Purpose—A pilot study to investigate the feasibility of the addition of intrathecal (IT) mafosfamide to a regimen of concomitant multi-agent systemic chemotherapy followed by conformal radiation therapy (RT) for children <3 years with newly diagnosed embryonal CNS tumors was performed.

Patients and Methods—Ninety-three newly diagnosed infants and children (<3 years) with embryonal CNS tumors were enrolled. Twenty weeks of systemic multi-agent chemotherapy commenced within 35 days of surgery. Patients without CSF flow obstruction (n=71) received IT mafosfamide (14 mg) with chemotherapy. Localized (M₀) patients with SD or better subsequently received RT followed by 20 additional weeks of chemotherapy. Second look surgery was encouraged prior to RT if there was an incomplete surgical resection at diagnosis.

Results—71 evaluable patients with normal CSF flow received IT Mafosfamide with systemic chemotherapy; patients with M+ disease were removed from protocol therapy at 20 weeks and

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those with PD at the time of progression. One and 5-year progression free survival (PFS) and overall survival (OS) for the cohort of 71 evaluable patients were $52\pm 6.5\%$ and $33\pm 13\%$, and $67\pm 6.2\%$ and $51\pm 11\%$, respectively. The 1-year Progression Free Survival (PFS) for M0 patients with medulloblastoma (MB, n=20), supratentorial primitive neuroectodermal tumor (PNET, n=9), and atypical teratoid rhabdoid tumor (ATRT, n=12) was $80\pm 7\%$, $67\pm 15\%$ and $27\pm 13\%$ and 5-year PFS was $65\pm 19\%$, $37\pm 29\%$, and $0\pm 0\%$, respectively.

Conclusion—The addition of IT mafosfamide to systemic chemotherapy in infants with embryonal CNS tumors was feasible. The PFS for M0 patients appears comparable to or better than most prior historical comparisons and was excellent for those receiving conformal radiotherapy.

Keywords

mafosfamide; intrathecal; infant brain tumor; embryonal CNS tumor; conformal radiation therapy

INTRODUCTION

The prognosis of infants and young children with embryonal CNS neoplasms, including medulloblastoma, supratentorial primitive neuroectodermal tumors (PNET), pineoblastoma, and atypical teratoid/rhabdoid tumors (AT/RT) is worse than for older children. Control of overt and microscopic leptomeningeal disease present at diagnosis in $>30\%$ of patients, is a major challenge to the successful treatment of younger children with embryonal CNS tumors.^{1–3} This propensity for widespread neuraxis dissemination of embryonal CNS tumors has resulted in the routine use of craniospinal irradiation (CSI) as a component of therapy in children older than 3 to 6 years of age. While CSI is an effective part of therapy in older children, it is associated with an unacceptably high incidence of neuropsychological and neuroendocrine sequelae in younger patients. As a result, since the mid-1980's treatment strategies for infants and young children with CNS tumors have primarily relied on the use of postoperative combination chemotherapy to delay or eliminate the need for radiation therapy (RT), potentially diminishing the age associated risks of developmental delays and intellectual deficits in these young patients.^{4–6} Although numerous studies have demonstrated the feasibility of post surgical chemotherapy, until recently, meaningful delay of RT has been achieved in only a minority of patients. Several recent reports have suggested that certain subsets of infants with medulloblastoma may have a good prognosis following surgery and chemotherapy without the addition of CSI.^{2,8}

In response to evolving issues in treating infants with malignant brain tumors, the Pediatric Brain Tumor Consortium developed a new therapeutic strategy utilizing a 20-week regimen of intensive systemic chemotherapy along with intrathecal (IT) chemotherapy followed by conformal RT and subsequent chemotherapy for infants with localized (M0) embryonal CNS tumors. We incorporated mafosfamide, a preactivated form of cyclophosphamide, as the IT component of therapy given the known antitumor activity of this alkylating agent in embryonal CNS tumors,^{9–12} in an attempt to obtain distant disease control without the use of CSI. This chemotherapy plus IT regimen was followed by conformal RT (Figures 1 and 2), if there was Stable Disease (SD), or better in an attempt to maximize local disease control.

For patients with initially localized disease (M0) treated with IT mafosfamide, secondary trial objectives included estimating the distribution of progression-free survival, documentation of acute and chronic toxicities, and estimating the proportion of patients in whom normal CSF flow was restored, if abnormal at diagnosis.

We previously reported results of the phase I component of this study in which the optimal mafosfamide dose was determined.¹³ We now report the final results of the feasibility and

efficacy component of this trial in which we assessed the feasibility of administering intrathecal mafosfamide to a 20-week regimen of intensive systemic chemotherapy.

PATIENTS AND METHODS

Patient Eligibility

Patients <3 years of age with newly diagnosed localized or metastatic medulloblastoma/PNET or other embryonal tumor, ATRT, intracranial germ cell tumor, choroid plexus carcinoma, or metastatic ependymoma were eligible. A Lansky performance score of $\geq 30\%$; and adequate bone marrow (Hgb ≥ 10 g/dl, ANC $\geq 1,500/\text{mm}^3$, and a platelet count $\geq 100,000/\text{mm}^3$, liver (serum bilirubin <1.5 mg/dl and SGPT <3 times the upper limit of normal) and renal function (normal serum creatinine for age or technetium clearance >40 ml/min/ m^2) were required. Patients could not have received prior therapy, with the exception of steroids, and were required to start protocol therapy within 35 days of surgery.

An additional criterion for entry was willingness to have a radionuclide CSF flow study (^{111}I -DTPA or ^{99}Tc -DTPA) to evaluate flow in the subarachnoid space. In patients without a ventriculoperitoneal (VP) or ventriculoatrial (VA) shunt, an Ommaya reservoir was required if the CSF flow study did not show evidence of obstruction or abnormal flow; after 2005, the protocol was amended to exclude patients with shunts. Those with a subarachnoid block did not receive mafosfamide, but could enter the trial and receive systemic chemotherapy; for such patients, a repeat CSF flow study following 8–10 weeks of therapy was required, and IT mafosfamide was introduced during the second 10 weeks of therapy if resolution of the block and normal CSF flow were demonstrated.

Informed consent was obtained from a parent or legal guardian in accordance with federal and local policies prior to study entry.

Studies Prior to and During Treatment

A complete history, physical and neurological examination, and laboratory studies were obtained before treatment. Pre-treatment CSF studies, from lumbar CSF in all patients and additionally from ventricular CSF in patients with Ommaya reservoirs included: cytology, cell count, protein, and glucose. Pre- and post-operative cranial MRIs ($\pm$ gadolinium) were obtained. The post-operative MRI was repeated if it had been obtained >3 weeks prior to the initiation of chemotherapy. A baseline MRI of the spine was obtained prior to surgery or 10 days after diagnostic surgery.

Physical and neurological evaluations were performed weekly $\times 6$ and during the first week of subsequent cycles of chemotherapy. Other regularly scheduled evaluations included laboratory studies, urinalysis, audiologic evaluations, and CSF studies. Neuroimaging was performed during weeks 10 and 20 of pre- and post-irradiation chemotherapy and approximately 4 weeks after the completion of RT.

Treatment

Chemotherapy was initiated within 35 days of definitive surgery. All patients received systemic chemotherapy, and patients without evidence of abnormal CSF flow received mafosfamide. M_0 patients with at least SD received conformal RT followed by 20 additional weeks of chemotherapy (Figure-2). All patients with metastatic disease were taken off therapy at week-20 and received further treatment per their primary oncologist's recommendations. Patients with progressive disease (PD) or unacceptable toxicity at any time were taken off therapy.

Intrathecal Mafosfamide—Mafosfamide (4-sulphoethylthio-cyclophosphamide L-lysine) was provided as 50 mg vials of freeze-dried compound initially by Asta Medica (Frankfurt, Germany) and subsequently by Baxter Pharmaceuticals (Frankfurt, Germany).

Mafosfamide, 14 mg, was administered twice weekly during weeks 1–6 (12 doses), weekly during weeks 7–9 (3 doses), and then every 3 weeks during weeks 11–17 (3 doses). It was administered in a final total volume of 5 mL of preservative-free saline at 0.5 ml/min in an isovolumetric fashion (i.e., an amount of CSF equivalent to the volume of drug to be administered was removed prior to injection). The site of administration was alternated between the intraventricular (intra-Ommaya) and intralumbar (via lumbar puncture) routes, except in patients with VP or VA shunts who received intralumbar dosing only. When drug was administered via an intraventricular reservoir, the reservoir was flushed slowly for 1–2 min with 2 ml of CSF or normal saline and then pumped 4–6 times. Following intralumbar drug administration patients were placed prone, in a flat or Trendelenburg position, for 1 hour.

Patients were premedicated with oral or IV dexamethasone (0.15 mg/kg, 6 to 12h and 1.5h) and morphine (0.1 mg/kg, IV 5 min) prior to IT mafosfamide. Patients who required general anesthesia for intralumbar drug administration received morphine after adequate recovery from anesthesia.

Pre-Irradiation Therapy – Regimen-1—All patients received 20 weeks of multi-agent chemotherapy with vincristine, cyclophosphamide, cisplatin and etoposide (Figure-2). Biopsy was encouraged at the completion of Regimen 1 chemotherapy in patients with residual radiographic abnormality suspicious for tumor. Similarly, surgical re-resection of local tumor was encouraged in patients with a partial (PR) response or SD at the completion of Regimen 1.

Radiation Therapy—M₀ patients with a complete response (CR), PR or SD received local conformal irradiation within 2 weeks of completing Regimen-1. The gross tumor volume (GTV) was defined as the contrast-enhancing tumor based upon pre-operative imaging and post-operative anatomic changes. For posterior fossa tumors, the initial Clinical Target Volume-Posterior Fossa (CTV-PF) encompassed the entire posterior fossa, and the Clinical Target Volume-Tumor Bed (CVT-T) was based on a 1.5 cm 3-dimensional expansion of the GTV, respecting anatomic boundaries. For supratentorial lesions, the GTV was similarly defined, and the initial CTV represented a 1.5 cm 3-dimensional expansion; the subsequent supratentorial boost was defined as a 1 cm expansion of the GTV. In all cases, an additional Planning Target Volume (PTV) was defined as a 3–5 mm strict geometric expansion of the relevant CTV. Supplementary Table-1 details radiation dose per PTV based on patient age, tumor location, and response to Regimen-1.

Post-Irradiation Chemotherapy – Regimen-2 (M0 Patients)—All patients with SD or better at the assessment 4 weeks following RT received 20 additional weeks of multi-agent chemotherapy as outlined in Figure-2.

Toxicity

Toxicities associated with mafosfamide and the systemic anticancer agents administered in this study were evaluated according to the Cancer Therapy Evaluation Program (CTEP) Toxicity Criteria version 2. If pain or flushing temporally related to the mafosfamide infusion was observed the infusion was stopped and subsequent doses were administered over a protracted time. In the event of reversible dose limiting toxicity attributable to IT

mafosfamide, a lower dose (11mg) was administered. If there was severe or life threatening neurotoxicity attributable to IT mafosfamide, then no further doses were administered.

Patients were removed from protocol therapy for any grade 3/4 non-hematologic toxicity as a result of chemotherapy, if it was not remediable with the dose reductions outlined in the protocol, with the exception of ototoxicity.

Statistical Considerations

The feasibility assessment included all eligible patients who received at least one dose of mafosfamide at the MTD from the phase 1 trial.¹³ Using the data from contemporary infant brain trials showing 30% or more of patients having PD by 20 weeks, the trial was designed to accrue 71 patients with three interim analyses by the method of Xiong¹⁴, where feasibility would have been rejected if 3 of 15 (20%); 13 of 35 (37%); or 35 of 71 (49%) patients successfully completed week 20 of therapy. This design provided 80% power ($\alpha=0.0449$) to detect a threshold of <45% of patients expected to successfully complete the first 20 weeks of therapy.

RESULTS

A total of 119 patients were registered on this trial from April 2001 to November 2005, of whom 115 were eligible. Following completion of the phase I component, 87 patients were enrolled on the feasibility component of the trial and per protocol design; six patients who were treated at the MTD during the phase I trial are included in the feasibility analyses. Twenty-two of the 93 patients were not evaluable for feasibility due to: abnormal CSF flow (n=10); no CSF flow study due to safety concerns (n=9); early disease progression (n=2); and withdrawal before receiving mafosfamide (n=1). Thus 71 of the 93 patients received mafosfamide and were fully evaluable for feasibility (See Figure-3). Patient characteristics of the 71 evaluable patients are shown in Table 1.

Based on the statistical design, the regimen was considered feasible; as 37 patients [52%; 95% CI (40%, 64%)] successfully completed the initial 20-weeks of therapy without PD. Fourteen additional patients completed the 20 weeks of therapy but had progressive disease at the week-20 assessment. Of the 14 patients with disease progression at week 20, four were M₀, and 10 were M+. Three of the four M₀ patients had local progression only and one had positive cytology. All of the M+ patients had local disease at the time of progression; 4 had positive spine imaging and 1 had indeterminate spine imaging; 5 had negative CSF lumbar cytology and in the other 5, cytology was not performed. The median number of mafosfamide doses administered per patient was 15 (range, 1–18) of 18 planned doses.

The Kaplan-Meier estimates of 1- and 5-year progression free survival (PFS) and overall survival (OS) for the cohort of 71 evaluable patients were 52±6.5% and 33±13%, and 67±6.2% and 51±11%, respectively (Supplementary Figure-1). The 1- and 5-year PFS rates for the targeted M₀ cohort of patients evaluable for feasibility with centrally reviewed histotypes of medulloblastoma (n=20); supratentorial PNET (n=9); AT/RT (n=12); and other histologies (n=6)] were 62.9±7 % and 41.3±14%. Similarly, 1- and 5-year OS rates were 76±6% and 60±12%, respectively. When evaluated by histologic subtype, the 1-year PFS for M₀ patients with medulloblastoma, sPNET and AT/RT were 80±7%, 67±15% and 27±13%, respectively; the 5-year PFS rates were 65±19%, 37±29%, and 0±0%, respectively.

Twenty seven (27) of the 47 M₀ patients (57%) received conformal RT per protocol; 15 (32%) progressed prior to the RT phase, and 5 (11%) did not receive RT by investigator and/or family decision.

Central histopathologic review was performed to investigate whether or not there was a correlation between “desmoplastic” histology and survival amongst those with medulloblastoma as has been reported by others.^{2,7} We found that the presence of nodular patterns, regardless of desmoplasia or anaplastic content, was associated with a favorable prognosis (Log-rank $p=0.015$).

Overall, the regimen was relatively well tolerated, with six patients requiring a mafosfamide dose reduction to 11 mg. The grade 2 or higher toxicities attributed (possibly, probably or definitely) to mafosfamide are shown in Table 2. The most common mafosfamide-associated adverse events were similar to those in the phase 1 trial and included irritability, and headache or pain during or immediately after drug administration. Two patients were removed from protocol therapy for mafosfamide-related adverse events, including one with agitation and headache and another with bradycardia and hypertension (grade 2) during the mafosfamide infusion. Four patients also experienced infections associated with their intraventricular access device, one of which was a fungal infection.

DISCUSSION

Treatment of infants with CNS tumors, particularly the prophylaxis and prevention of leptomeningeal dissemination without the use of craniospinal RT, remains a challenge. In an attempt to maximize survival while minimizing the neuroendocrine and neuropsychological morbidity associated with craniospinal RT, we developed a treatment strategy that we hypothesized would provide both maximum local and distant disease control using conformal RT plus IT therapy, respectively. Although these results suggest that administration of IT mafosfamide within the context of the PBTC-001 study did not appear to significantly affect patient outcome, the 5-year PFS and OS rates of 71 evaluable patients in this study ($33\pm12\%$ and $51\pm11\%$, respectively) are similar to those observed in historical studies such as the Children’s Cancer Group (CCG)-9921 trial (5-year PFS $27\pm3\%$ and OS $43\pm3\%$)¹⁵ and the German HIT trial (PFS 58% and OS 68%)¹⁶ and the Australian and New Zealand ANZCCSG BabyBrain99 study (5-year OS 40%).¹⁷ The relatively similar results between these intensive, yet disparate, treatment regimens suggests that there may be a specific underlying tumor biology that renders some infant embryonal tumors more responsive to therapy than others. Although several recent infant trials have suggested that the subset of infants with desmoplastic medulloblastoma have a superior outcome,^{2,8} cohort of patients treated on PBTC-001 and diagnosed with M0 medulloblastoma by central pathology review showed that a nodular pattern, not desmoplasia by itself, is associated with improved survival for infants.¹⁸

The toxicities associated with IT mafosfamide were similar to those observed on the previously reported phase 1 trial with irritability and pain that were temporally associated with drug administration the most commonly observed.¹³ In the context of an intensive regimen of systemically administered multi-agent chemotherapy, a newly diagnosed primary CNS tumor, and general anesthesia for intra-lumbar administration, it was often difficult to ascertain whether adverse events such as nausea/vomiting, seizures, or weight loss, were related to IT mafosfamide, another component of the therapy, or the entire treatment regimen. Nevertheless, all of the acute adverse events that were observed appeared to be fully reversible.

In summary, we have demonstrated that it is feasible to administer IT chemotherapy to the majority of infants with newly diagnosed embryonal CNS tumors. Unfortunately, the addition of IT mafosfamide did not appear to have a clear beneficial impact on patient outcome, although this trial was not designed to specifically address that question. Since mafosfamide is no longer available for patient use, this particularly question will remain

unanswered. However, since drug delivery to the entire CNS neuraxis will be an ongoing challenge for the treatment of a large subset of children with medulloblastoma, it is important to know that frequent delivery of IT therapy with concomitant intensive combination chemotherapy is possible for the majority of infants with newly diagnosed CNS tumors.

Interestingly, the survival for infants with M0 medulloblastoma who received local XRT was excellent. The 5-year OS for this subgroup of infants was $90\pm 10\%$, results that are at least equivalent to, if not better than, previously reported subgroups. We cannot correlate this high survival rate with desmoplastic histology, as reported by other investigators. Nevertheless, these results suggest that there is a subgroup of infants with medulloblastoma who may have an excellent long-term outcome without adjuvant craniospinal RT. Ongoing studies to confirm this finding and to learn more about the biology of embryonal CNS tumors of infancy and early childhood are in progress.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Study Scheme

Figure 2.
 Details of Therapy Schedule during Course-1 and Course-2

MB: Medulloblastoma

Figure 3.
Patient Flow Diagram

Table 1

Patient Characteristics (N=93)

		Evaluable for Feasibility		Not Evaluable for Feasibility		All Patients		
		N	%	N	%	N	%	
GENDER	Female	33	46.5	8	36.4	41	44.1	
	Male	38	53.5	14	63.6	52	55.9	
	Unknown	5	7.0	2	9.1	7	7.5	
ETHNICITY	Hispanic or Latino	7	9.9			7	7.5	
	Non-Hispanic	59	83.1	20	90.9	79	84.9	
	Asian	2	2.8			2	2.2	
RACE	Black	5	7.0	3	13.6	8	8.6	
	Unknown	5	7.0			5	5.4	
	White, Non-Hispanic	59	83.1	19	86.4	78	83.9	
M STAGE and DIAGNOSIS	M ₀	Medulloblastoma	20	28.2	6	27.3	26	28.0
		PNET [*]	9	12.7	1	4.5	10	10.8
		ATRT [^]	12	16.9	1	4.5	13	14.0
		Other	6	8.5	2	9.1	8	8.6
	M ⁺	Medulloblastoma	10	14.1	7	31.8	17	18.3
		PNET	1	1.4	1	4.5	2	2.2
		ATRT	8	11.3	3	13.6	11	11.8
		Other	5	7.0	1	4.5	6	6.5
Total		71	100.0	22	100.0	93	100.0	

^{*} PNET - supratentorial primitive neuroectodermal tumor[^] ATRT 0 atypical teratoid rhabdoid tumor

Table 2

Number of adverse events possibly, probably or definitely related to mafosfamide

Adverse Event	Grade 2	Grade 3	Grade 4
Apnea		1	
Arachnoiditis	1	2	
Irritability, agitation/pain with infusion	12	8	
Cerebral edema	1		
Cranial nerve palsy	4	1	
Dehydration	2		
Depressed level of consciousness	2	1	
Fever		1	
Hallucination		1	
Headache	3	7	
Hypertension	2		
Hypothermia	1		
Hypoxia			1 *
Increased CSF protein	1		
Nausea/vomiting	13	1	
Skin discoloration/rash	2	1	
Seizure	2	2	
Speech impairment	2		
Voice changes	4	1	
Weight loss	1		

* Patient briefly intubated secondary to hypoxia associated with coughing and emesis during mafosfamide administration