Neuro-Oncology

22(11), 1696–1704, 2020 | doi:10.1093/neuonc/noaa119 | Advance Access date 12 May 2020

Phase II study of peginterferon alpha-2b for patients with unresectable or recurrent craniopharyngiomas: a Pediatric Brain Tumor Consortium report

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Abstract

Background. Craniopharyngiomas account for approximately 1.2–4% of all CNS tumors. They are typically treated with a combination of surgical resection and focal radiotherapy. Unfortunately, treatment can lead to permanent deleterious effects on behavior, learning, and endocrine function.

Methods. The Pediatric Brain Tumor Consortium performed a multicenter phase 2 study in children and young adults with unresectable or recurrent craniopharyngioma (PBTC-039). Between December 2013 and November 2017, nineteen patients (median age at enrollment, 13.1 y; range, 2–25 y) were enrolled in one of 2 strata: patients previously treated with surgery alone (stratum 1) or who received radiation (stratum 2).

Results. Eighteen eligible patients (8 male, 10 female) were treated with weekly subcutaneous pegylated interferon alpha-2b for up to 18 courses (108 wk). Therapy was well tolerated with no grade 4 or 5 toxicities. 2 of the 7 eligible patients (28.6%) in stratum 1 had a partial response, but only one response was sustained for more than 3 months. None of the 11 stratum 2 patients had an objective radiographic response, although median progression-free survival was 19.5 months.

Conclusions. Pegylated interferon alpha-2b treatment, in lieu of or following radiotherapy, was well tolerated in children and young adults with recurrent craniopharyngiomas. Although objective responses were limited, progression-free survival results are encouraging, warranting further studies.

Key Points

1. Pegylated interferon alpha-2b is well tolerated in patients with recurrent craniopharyngiomas.
2. Objective responses are rare, but progression-free survival data warrant further studies.

Importance of the Study

Craniopharyngiomas are a type of rare brain tumor that affect predominantly children. The current standard of care is either partial surgical resection of the tumor followed by radiotherapy, or complete resection, which is extremely challenging given the proximity of the tumor to vital brain regions, including the optic chiasm. Both treatment approaches, unfortunately, are associated with severe and lifelong adverse consequences on behavior, learning, vision, and endocrine function in patients. Thus, there is an urgent need to find safe and effective therapies to treat craniopharyngiomas. Here, we report a phase II study of pegylated interferon alpha-2b for children and young adults with unresectable or recurrent craniopharyngiomas. Systemic administration of peginterferon alpha-2b, either in lieu of or following radiotherapy, was well tolerated. Though limited by small sample size and short follow-up, progression-free survival rates compare well with historical data on experimental treatments for craniopharyngiomas, warranting further studies.

Craniopharyngiomas account for 1.2–4% of all primary brain tumors, and 5–10 % of brain tumors in children.[1] They arise from neoplastic transformation of epithelial cell remnants from adenohypophysis development. The adenomatous subtype of craniopharyngioma is prevalent in childhood, while the squamous papillary subtype is rarely seen in children.[2] Craniopharyngiomas present as a single large cyst or multiple cysts filled with a proteinaceous material along with a variable-sized solid component.[3–7] Although histologically benign, these tumors are functionally malignant due to their proximity and frequent adherence to the optic chiasm, third cranial nerve, hypothalamus, and internal carotid arteries and their branches, which limits safe and complete surgical resection. Attempts to achieve substantial resection are often accompanied by significant morbidity, with recurrence rates ranging from 22% to 50%.[8–10] Prognosis with subtotal resection and external beam radiotherapy is comparable to that with complete resection.[11–13] Therefore, either approach is considered the standard of care.[14–16]

Unfortunately, treatment can lead to permanent deleterious effects on behavior, learning, vision, and endocrine function.[17,18] The vast majority of treated children suffer from multiple endocrinopathies. The effects of hypothalamic damage, including hypothalamic obesity, impaired socialization, and poor academic performance ("hypothalamic syndrome"), are often lifelong and difficult to manage and treat. Therefore, there is a great unmet need for alternative treatment approaches.

Sequencing analyses have revealed near universal mutations of catenin beta-1 (*CTNNB1*) in adamantinomatous craniopharyngiomas, whereas *BRAFV600E* mutations are frequently found in papillary craniopharyngiomas indicating activation of the mitogen-activated protein kinase (MAPK) signaling pathway.[19] The WNT/beta-catenin pathway prevents differentiation of mouse embryonic stem cells through convergence on the leukemia inhibitory factor/Janus kinase–signal transducers and activators of transcription (JAK-STAT) pathway.[20,21] Interferons are known activators of JAK/STAT pathways. Interferons are a family of naturally occurring small proteins secreted by eukaryotic cells in response to viral infections, and exert their antitumor activity through direct anti-proliferative and cytotoxic effects, and through modulation of the host immune response.[21] When administered systemically or directly into a lesion, interferon-alpha has shown significant activity against squamous cell skin carcinoma,[22] which is believed to have the same embryologic ectodermal origin as craniopharyngiomas. Pegylated interferon, which has a longer half-life and more sustained tumor exposure than non-pegylated interferon,[14,23–25] was better tolerated than non-pegylated interferon in a recent pilot study of 5 pediatric patients with progressive or recurrent craniopharyngiomas.[14,26] All 5 patients had responses, with 2 achieving complete response.

Based on these findings, a phase II study of pegylated interferon alpha-2b was developed by the Pediatric Brain Tumor Consortium (PBTC) for children and young adults with unresectable or recurrent craniopharyngiomas (PBTC-039, NCT01964300).

Patients and Methods

Patients

Patients aged 18 months to 25 years with progressive or recurrent unresectable craniopharyngiomas were enrolled on one of 2 strata. Stratum 1 included those

patients previously treated with surgery alone and who had never received radiotherapy. Stratum 2 included those patients who had previously received radiotherapy. All subjects were required to have a histologic diagnosis of craniopharyngioma, without evidence of metastatic lesions. To avoid enrollment of patients who might still be responding to radiotherapy or might exhibit radiographic "pseudoprogression," stratum 2 patients were required to be at least 6 months post-irradiation (including Gamma Knife, intracavitary radioactive phosphorus-32 chromic phosphate (^{32}P), or external beam radiotherapy) if the tumor was predominantly solid, or 12 months post-irradiation if the tumor was predominantly cystic. All patients were required to have measurable disease for both the cystic and solid components in 2 perpendicular diameters on MRI. In addition, patients could not have received prior interferon, could not be receiving steroids other than physiologic replacement doses, and needed to have evidence of normal bone marrow, liver, and renal function. Informed consent was obtained from all patients and the study was approved by the institutional review boards at each institution.

Study Treatment

Patients were required to begin therapy within 7 days of registration. All patients were administered a weekly subcutaneous injection of pegylated interferon alpha-2b (either PEG-Intron or Sylatron, based on availability) at a dose of 1 μg/kg/week; 6 weekly doses constituted a course, and treatment could continue without break for up to 18 courses. During the study, PEG-Intron vials for subcutaneous use were discontinued for distribution in the USA by Merck and were replaced by Sylatron. This change was not reflective of any safety or efficacy findings. Sylatron consists of the same active ingredient as PEG-Intron at a different dosage strength. This change was reviewed and approved by the National Cancer Institute and the local institutional review boards and did not require any other changes to the treatment protocol.

Patients and/or parents were taught to administer the medication in the outpatient setting and were asked to keep a diary to document weekly drug administration and any symptoms. Given that the expected constitutional symptoms (eg, fatigue, malaise, fever) are generally the most severe after the first few doses, acetaminophen was given 30 minutes prior to administration of the first 6 doses and prior to subsequent doses as needed. Any fever that developed after a dose of pegylated interferon was treated with acetaminophen alternating with ibuprofen. Treatment continued weekly without a break in the absence of disease progression or unacceptable toxicities. If any course was delayed for more than 21 days due to persistent, unacceptable drug-related toxicity, the subject was taken off protocol therapy.

Tests and Examinations

Baseline brain MRI scans were performed on each patient with thin, high-resolution images through the suprasellar/sellar region with and without contrast consisting of sagittal and coronal T1 images, axial T2 fluid attenuated inversion recovery, axial T2, coronal T2, and post-contrast T1 through the whole brain. A complete history was taken and physical examination performed at baseline, including visual fields if feasible, standard laboratory evaluations, urine protein evaluation, and a pregnancy test for females of childbearing potential. Tumor assessments by MRI were to be obtained at baseline, every 12 weeks during the first year of treatment, and every 18 weeks thereafter until there was evidence of disease progression, unacceptable toxicity, or completion of 18 courses, which is approximately 2 years of therapy. Table of assessments and definitions of radiographic progression are provided in Appendixes 1 and 2, respectively.

Response Criteria

Defining response and progression in craniopharyngioma can be challenging due to the frequent co-occurrence of cystic and solid components. Therefore, the definitions of progressive disease (PD) were different from the McDonald criteria for both strata, in keeping with recent efforts to reassess definitions of clinically relevant response criteria for unique pediatric brain tumors.[27] The McDonald criteria, originally utilized for adult glioblastoma multiforme, defines PD as greater than 25% increase in the enhancing components of the tumor. For this study, linear 2D measurements of the solid and cystic components were required. For both strata, during the first 12 months of treatment, surveillance images were compared with the smallest disease measurement recorded since the start of protocol. PD was defined as: (i) greater than or equal to 25% increase in the product of the greatest perpendicular diameters of the solid component and ≥0.4 cm increase in each of at least 2 dimensions of the solid component since the start of the protocol treatment; (ii) any new or worsening significant neurologic/vision deficit in conjunction with a lesser change in the solid component; or (iii) any new or worsening significant neurologic/vision deficit associated solely with a change in the cystic component that did not at least stabilize following a simple cyst aspiration. Isolated cystic enlargement was not considered PD during the first 12 months of treatment unless more than one cyst aspiration was required for symptom control. Linear 2D measurements of the solid and cystic components were obtained.

After the first 12 months of treatment, progression was defined as: (i) greater than or equal to 25% increase in the product of the greatest perpendicular diameters of the tumor as a whole (solid and cystic component) and ≥0.4 cm increase in each of at least 2 dimensions of the tumor as a whole compared with the smallest disease measurement recorded since the start of protocol treatment; or (ii) any new or worsening significant neurologic/vision deficit in conjunction with a lesser change in the tumor as a whole. If cyst aspiration was required for symptom control, the patient was considered to have PD. Volumetric analyses of the solid and cystic components were also obtained using a Vitrea workstation (Vital Images).

Pathology

Central review of tumor histopathology was required if sufficient tissue was available. Starting with protocol Amendment 4, tissue submission and review became an eligibility requirement. Any additional formalin-fixed paraffin-embedded (FFPE) unstained slides were submitted for immunohistochemistry analyses of beta-catenin nuclear expression, which is a biomarker for assessing WNT pathway activation, and pyrosequencing for determining *BRAFV600E* status, which indicates MAPK pathway activation.

Representative sections of the submitted slides were stained with hematoxylin and eosin to determine the presence of adequate tumor component for immunohistochemical staining and subsequent analyses. Tissue sections were deparaffinized in xylene, followed by graded hydration in 100% and 70% ethanol to H_2O. Antigen retrieval was done by boiling in 10-mmol EDTA. Endogenous peroxidase was blocked with 3% H_2O_2/methanol. Sections were incubated with 1:6 dilution of monoclonal anti–beta-catenin antibody (Leica; catalog #PA0083, clone 17C2) using the "bond polymer refine detection kit" as per manufacturer's (Leica) instruction with DAB (3,3′-diaminobenzidine) as a chromogen.

Immunohistochemical staining was graded by intensity as mild, moderate, or strong and by extent of positivity into the following groups: rare to few positive individual nuclei or rare nuclear cluster only (less than 10%), moderate number of nuclei (>10% ≤25%), frequent number of positive nuclei (>25% ≤50%), and widespread nuclear positivity (>50%).

To identify papillary craniopharyngiomas, which are characterized by frequent *BRAFV600E* mutations, PCR was performed on DNA extracted from FFPE tissue using *BRAF* gene specific primers encompassing codon 600. Amplified PCR products were then subjected to pyrosequencing using a PSQ96 instrument and analyzed using PSQ96 AQ software (Qiagen). Samples showing >15% mutant allelic frequency were interpreted as positive for *BRAFV600E* mutation.

Primary Endpoints

For stratum 1, the primary objective was to estimate the one-year disease stabilization rate associated with the use of pegylated interferon for patients with progressive unresectable or recurrent craniopharyngioma who had not previously received radiotherapy. For stratum 2, the primary objective was to estimate the sustained objective response rate (partial response [PR] + complete response [CR]) to pegylated interferon in patients whose craniopharyngiomas progressed or recurred following radiotherapy. Tumor response was measured using either T1- or T2-weighted MR images. CR was defined as the total disappearance of all radiographically detectable tumor sustained on a follow-up scan performed at a minimum of 3 months later. PR was defined as at least a 50% decrease in the product of the greatest perpendicular diameters of the tumor as a whole (solid and cystic components) that was sustained on the follow-up scan for a minimum of 3 months. PD definition varied by the strata and the time of treatment, taking into account the frequently encountered transient increase in cyst size that can be seen both during interferon therapy as well as for a prolonged period of time after radiotherapy as described in the "Response Criteria" (Appendix 2).

Secondary Endpoints

Secondary endpoints included sustained objective response rate and progression-free survival (PFS) in both strata, evidence of WNT and MAPK pathway activation in resected tumor, and description of toxicity in this population.

Statistical Methods

The primary endpoint for stratum 1 was the percentage of patients who completed 9 courses of treatment (approximately 1 year) without an event (disease progression or death for any reason). Due to the lack of reliable historical clinical data in pediatric craniopharyngioma, a one-sample, one-sided exact binomial design was used. The design deemed peginterferon alpha-2b not worthy of further investigation in this patient population, if the true 1-year disease stabilization rate was less than 50% with a 90% statistical power to detect a true disease stabilization rate of 75%. These parameter settings and a 10% type I error rate led to a sample size of 28 patients. If 18 or more patients experienced disease stabilization that lasted for at least 1 year, then we would conclude that the agent was sufficiently active in this disease to warrant further investigation. An interim analysis for futility was planned after 12 patients had been enrolled and followed for 1 year (accrual was not stopped for interim analysis). Seven or more patients with 1-year disease stabilization were required to expand accrual beyond the interim analysis.

The design for stratum 2 was based on Simon's optimal two-stage design where objective response rate observed during the first 9 courses was the primary endpoint. To count toward the success criteria, objective responses had to be sustained for 3 months. The design was calibrated for undesirable response rate of 10% and a promising response rate of 35%. These parameter settings with 10% type I and II error rates led to a sample size of 19 patients, with 11 patients to be accrued in the first stage. Two or more responses were needed in the first 11 patients to expand accrual, and 4 or more sustained objective responses would suggest promising activity.

PFS was defined as the interval from date of treatment initiation to the earliest date of disease progression, second malignancy, or death for any reason, or to the date of last contact for patients who remained at risk for failure. PFS distributions were estimated using the Kaplan–Meier method; standard errors were calculated using the method of Peto and Pike.[28] The exact Wilcoxon rank sum test was used to examine the association between age and stratum. For toxicities observed in greater than 5% of cycles, repeated measures models were used to examine associations between agent (PEG-Intron or Sylatron) and toxicity (any grade).

Results

Patient Characteristics

Between December 20, 2013 and November 16, 2017, eighteen eligible patients were enrolled: 7 in stratum 1 and 11 in stratum 2. One additional stratum 2 patient was deemed ineligible due to a concurrent malignancy. All eligible patients began study treatment and were considered evaluable for the primary objectives. As anticipated, the median age at study entry was lower for stratum 1 patients (who had not previously received radiotherapy) compared with stratum 2 patients (who progressed post-radiotherapy). Median age was 10.6 years (range, 2.0–17.0 y) for stratum 1 versus 20.5 years (range, 6.1–25.0 y) for stratum 2 ($P = 0.022$) (Table 1). At the time of study entry, all patients had a histologic diagnosis of craniopharyngioma established by the institution. Among the 18 eligible patients, 14 were subtyped as adenomatous craniopharyngioma and 4 were reported as craniopharyngioma with no subtyping.

Treatment

A total of 141 cycles (6 weekly injections planned per cycle) were administered during the study. PEG-Intron was administered for 87/141 cycles (62%) and Sylatron for 52 cycles (37%). The remaining 2 cycles (in 2 patients) began with PEG-Intron but then changed to Sylatron due to availability. Both patients continued to receive Sylatron in subsequent cycles. The median number of cycles of therapy received in stratums 1 and 2 was 4 (2–18) and 6 (1–18), respectively (Table 2).

Toxicities

Toxicities were graded using the Common Terminology Criteria for Adverse Events version 4.[29] The most frequently reported toxicities were grades 1 and 2, with decreased white blood cells and neutrophils, elevated alanine aminotransferase (ALT)/aspartate aminotransferase, and fever. There were 12 grade 3 toxicities over the 141 cycles given. Two subjects (11%) experienced a total of 4 episodes of grade 3 neutropenia and 1 patient (5.5%) experienced 2 episodes of grade 3 increase in ALT. Grade 3 nausea, fatigue, anorexia, fever, headache, and oral mucositis were reported as single episodes. No grade 4 or 5 toxicities were reported. Two of the 18 patients came off therapy due to toxicity: one patient (stratum 2) refused further study treatment secondary to grade 2 flu-like symptoms after receiving only a single dose of peginterferon, and another patient (stratum 1) came off treatment after 3 cycles due to grade 3 ALT elevation. One additional patient in stratum 2 was dose-reduced during cycle 5 secondary to grade 3 anorexia (from 1 μg/kg/week to 0.6 μg/kg/week) and continued at the reduced dose from cycles 6 through cycle 14.

Table 1 Patient characteristics for eligible patients, by stratum

	Stratum				All Patients	
	Stratum 1		Stratum 2			
	n	%	*n*	%	*n*	%
Age, y, at diagnosis						
Median	9.3	–	7.0	–	7.7	–
Minimum	0.3	–	2.0	–	0.3	–
Maximum	14.9	–	12.4	–	14.9	–
Age, y, at enrollment						
Median	10.6	–	20.5	–	13.1	–
Minimum	2.0	–	6.1	–	2.0	–
Maximum	17.0	–	25.0	–	25.0	–
Sex						
Male	3	42.9	5	45.5	8	44.4
Female	4	57.1	6	54.5	10	55.6
Race						
White	4	57.1	8	72.7	12	66.7
Black or African American	0	0	2	18.2	2	11.1
Unknown	3	42.9	1	9.1	4	22.2
Ethnicity						
Hispanic or Latino	2	28.6	2	18.2	4	22.2
Non-Hispanic	4	57.1	7	63.6	11	61.1
Unknown	1	14.3	2	18.2	3	16.7

Table 2 Number of cycles by stratum for eligible patients

	Stratum 1 ($n = 7$)	Stratum 2 ($n = 11$)
Median # of cycles given	4	6
Minimum # of cycles given	2	1
Maximum # of cycles given	18	18
Total # of cycles given	54	87
# given as PEG-Intron	20	67
# given as Sylatron	34	18
# given as a combination	0	2

The majority of constitutional symptoms (fatigue, anorexia, fever, and myalgia) occurred in the first 2 months of therapy. The only significant difference in toxicities observed between PEG-Intron and Sylatron cycles was neutropenia, which occurred in 23 of 87 PEG-Intron cycles (26%) and 4 of 52 Sylatron cycles (8%) ($P = 0.005$). A full list of toxicities is included in Appendix 3.

Response

Stratum 1.—Two of the 7 patients (28.6%) on stratum 1 (both with predominantly cystic tumors) had a PR, but only one was sustained on imaging for more than 3 months (1/7, 14.3%) (Figure 2). Thus, only 1 patient met the protocol-defined definition of PR. An interim analysis was planned after enrollment of a twelfth patient, but due to slow accrual, stratum 1 was closed prematurely.

Stratum 2.—Eleven patients were enrolled to stratum 2. Five patients received at least one year of treatment. Of the remaining 6 patients, 1 came off treatment after only one dose of PEG-Intron due to flu-like symptoms; 3 patients came off treatment due to progression after 6 cycles ($n = 2$) or 3 cycles ($n = 1$); 1 patient withdrew after 2 cycles with no specific reason noted, and 1 patient came off treatment during cycle 4 for a procedure not allowed by protocol. None of the 11 patients attained the primary endpoint of objective radiographic response, and the study was closed to further accrual after the planned interim analysis.

Progression-Free Survival

As of January 30, 2019, no deaths have been reported. The median follow-up from start of treatment for stratum 1 patients was 6.2 months (5.2–24.9) and the median follow-up for stratum 2 patients was 12.9 months (3.2–25.7). Three of the 7 patients in stratum 1 have progressed at a median of 13.5 months (5.4–17.7) from treatment initiation (during cycles 4, 10, and 13). Two patients with PD had primarily solid component growth and 1 patient had progression of both the cystic and solid components. One- and 2-year PFS estimates were 83.3 ± 17.0% and 27.8 ± 16.7%, respectively (Fig. 1). Five of 11 stratum 2 subjects progressed, 2

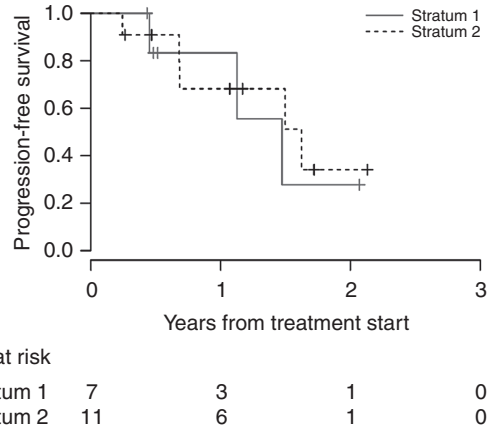

Fig. 1 Progression-free survival for eligible patients by stratum. PFS for stratum 1 and stratum 2 from start of peginterferon alpha-2b treatment.

with primarily cystic progression, 1 with primarily solid progression, and 2 with mixed cystic and solid progression. PD occurred at a median of 8.2 months (2.9–19.5) from the start of treatment. One- and 2-year PFS estimates were 68.2 ± 14.5% and 34.1 ± 19.6%, respectively (Figure 1). Based on the Kaplan–Meier method, the median times to progression were 17.7 months and 19.5 months for stratum 1 and stratum 2, respectively.

Biologic Correlates

Five of 7 stratum 1 and 10/11 stratum 2 patients submitted biology samples for testing. All 15 (100%) cases had wild-type *BRAF* with no demonstrable mutation. Thus a positive or negative impact of *BRAFV600E* mutation on outcome could not be explored. Four of 5 stratum 1 samples (80%) and 9/10 stratum 2 samples (90%) showed strong staining (+++) for beta-catenin. The effect of beta-catenin mutation/WNT pathway activation on outcome could not be determined given our patient numbers.

Discussion

Craniopharyngiomas are rare CNS tumors with a bimodal age distribution with peaks in childhood (5–14 y) and in adults older than 65 years. They account for approximately 4% of all intracranial tumors, 5–10% of childhood intracranial tumors, and approximately 56% of sellar/suprasellar tumors in children.[30] Despite the often "life-altering morbidity" that patients suffer as a result of treatment,[17,18] only a limited number of novel chemotherapeutic trials have been reported.

Craniopharyngiomas have 2 major histologic subtypes: papillary and adamantinomatous. Adamantinomatous craniopharyngiomas exhibit peaks at ages 5 to 15 years and 45 to 60 years.[19] In comparison, papillary craniopharyngiomas occur almost exclusively in adults,

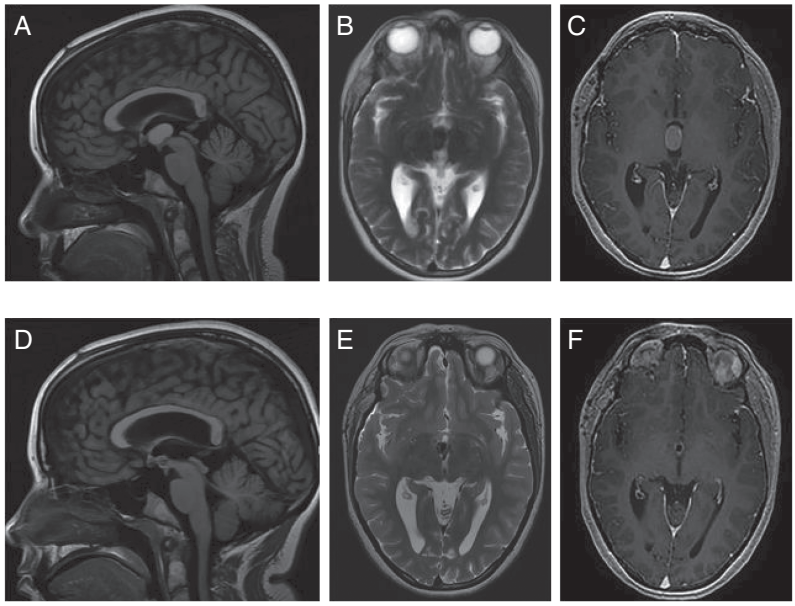

Fig. 2 Imaging for an individual stratum 1 patient with a partial response. Pre-therapy sagittal T1 demonstrates a hyperintense lesion in the suprasellar region extending into the third ventricle (A). Axial T2 demonstrates a hypointense lesion in the third ventricle (B) and post-contrast axial T1 demonstrates minimal peripheral enhancement in the third ventricular mass (C). Post-therapy sagittal T1 2 years later demonstrates that the heterogeneous mass in the suprasellar region/inferior third ventricle is smaller in size (D). Axial T2 demonstrates the hypointense lesion with decrease in tumor size (E) and post-contrast axial T1 demonstrates ring enhancing lesion in the third ventricle, decreased in size (F).

at a mean patient age of 40 to 55 years.[19] Recent studies have identified *BRAFV600E* mutations in the papillary variant of craniopharyngiomas, offering promising options for targeted therapy, especially given the development of direct BRAF inhibitors. For adamantinomatous variants, the β-catenin and WNT pathway protein, CTNNB1, is frequently mutated, and further work is under way to identify new therapeutic targets.[31]

As noted previously, a 5-year PFS of 65–80% has been reported for gross totally resected tumors, whereas the 5-year PFS in patients who undergo subtotal resection (with the goal of decompressing the optic chiasm and confirming the diagnosis) followed by radiotherapy is ~70–90%.[10,19] Both treatment approaches can result in significant hypothalamic damage with similar rates of life-altering neurologic, visual, metabolic, and endocrine disorders.[3] In a 10-year follow-up of children with craniopharyngioma treated in Switzerland, 45% developed hypothalamic obesity, 66% had diabetes insipidus, and 53% had pathologically low bone density.[32] Nonstandard treatment approaches to either avoid or delay the use of radiotherapy or to treat for progression following radiotherapy have yielded disappointing results.[33]

Childhood craniopharyngiomas are predominantly cystic lesions, explaining the preponderance of studies evaluating intracystic therapies.[34] Shazadi et al reported on ^{32}P, which destroys the epithelial lining of the cyst wall.[35] Approximately 40% of pediatric and adult patients, the majority of whom had a predominantly cystic tumor, required only one treatment with a reported response rate of 78%. Complications related to the therapy included CSF leakage from a scalp wound, a brain abscess, a superficial wound infection, and a transient sixth cranial nerve palsy.[35] Similarly, 53 patients were treated with intracavitary/intracystic ^{32}P for cystic craniopharyngioma at either diagnosis or recurrence. Visual function improved in 23.5%, was unchanged in 66.7%, and worsened in 9.8% of the cases; 19.6% of the patients also had worsening endocrinologic function, showing that any damage to the hypothalamic area, regardless of how it is induced, can be functionally deleterious.[36] Other groups have used intracavitary radioisotopes, including yttrium-90, rhenium-186, and aurum-198[37] and chemotherapeutic agents such as intratumoral bleomycin, which was ineffective in mixed cystic/solid craniopharyngiomas but effective in predominantly cystic craniopharyngiomas.[38]

Further studies have shown some efficacy with intracystic therapy (CR rates of 29–67% in children), although it is generally short-lived.[34,39] Intracystic bleomycin is usually well tolerated; however, significant morbidity and mortality have been associated with bleomycin leakage, including transient and persistent seizures, hemiparesis, hypothalamic injury, blindness, and death.[34,40,41]

The use of interferon-alpha as an intracystic therapy was first reported by Cavalheiro in 2005.[42] In a large European series of 60 children treated with intracystic interferon alpha, 78% of patients had greater than a 50% cyst shrinkage; however, 22% who had PD required

repeat surgical intervention after intracystic therapy.[43] The European International Society of Pediatric Oncology (SIOPE) and the International Society of Pediatric Neurosurgery (ISPN) retrospectively evaluated the use of intracystic interferon alpha in 56 children, including patients with newly diagnosed and recurrent craniopharyngiomas with a cystic component. Thirty-nine percent of the lesions were either purely or predominantly cystic, and 61% were both cystic and solid. Intracystic interferon therapy was the initial treatment for 13/56 patients (23%); the remaining had numerous previous therapies, including cyst aspiration/fenestration, tumor excision, focal radiotherapy, and radioisotope therapy. Patients received a median of 14 (6–84) doses of intracystic alpha interferon. Patients with predominantly cystic lesions who had undergone previous treatment had a significant delay in progression following interferon treatment compared with the preceding therapy ($P = 0.0005$). Patients with solid/cystic lesions had no delay in progression. The median time to definitive therapy post-interferon was 5.8 years (1.8–9.7). At a median follow-up of 2.7 years, 14/56 (25%) children had no evidence of disease progression and 51/56 (91%) patients remained alive; 2 patients died of disease progression.[3]

Jakacki and colleagues reported safety and efficacy with weekly subcutaneous injections of pegylated interferon alpha-2b in young patients with unresectable plexiform neurofibromas.[44] The same group reported on systemic interferon alpha treatment of 5 children with recurrent craniopharyngiomas, all of whom had stable disease or better, including 1 with a PR, and 2 with a CR who remain disease free at last follow-up and have not required additional therapy.[26] The responses were almost exclusively in the cystic component.[45]

The current study was designed to estimate sustained objective response rates in stratum 2 patients whose progressive craniopharyngiomas recurred following radiotherapy. Although PFS was not the primary endpoint, the one-year PFS was 68.2% ± 14.5% with a median time to progression of 19.5 months, and our data compare favorably to the historical studies noted above. Stratum 1 patients also exhibited a promising one-year PFS of 83.3% and a median time to progression of 17.7 months. Unfortunately, this stratum had to close prematurely due to poor accrual, and the PFS could change significantly over time given the small numbers. Two patients, however, had PR, one after 2 courses, which was maintained throughout treatment. The second patient was taken off treatment on week 2 of cycle 2 due to enlargement of the cyst with a grade 3 catheter-related infection and subsequently underwent proton beam radiotherapy. Due to the small sample sizes and the short follow-up, these results are preliminary. Further trials should be developed to study subcutaneous interferon treatments for patients with recurrent craniopharyngiomas, using PFS, and not response, as the primary endpoint.

In conclusion, in children and young adults with recurrent craniopharyngiomas, the use of systemic pegylated interferon alpha-2b, in lieu of radiation or following radiotherapy, was well tolerated. The major side effects and expected toxicities were constitutional symptoms, which generally improve with time. Although objective responses were limited, PFS results are encouraging. Further studies, particularly in primarily cystic, adamantinomatous craniopharyngiomas, are warranted.

Keywords

craniopharyngioma | interferon | pediatric brain tumor | peginterferon alpha-2b

Funding

This study was supported by the National Cancer Institute Cancer Therapy Evaluation Program PBTC U01 grant UM1CA081457, the MSKCC Core Grant P30 CA008748, and the American Lebanese Syrian Associated Charities (ALSAC), which provides funding and infrastructure support for the Pediatric Brain Tumor Consortium Operations Core personnel. Merck provided peginterferon alpha-2b and Sylatron for the study and funded its distribution.

Acknowledgments

We thank Agila Somasundaram for editorial assistance with the manuscript. This work was presented at the 2018 International Society of Pediatric Neuro-Oncology meeting in Denver, Colorado.

Conflict of interest statement. S.G. declares consultant roles for Novartis and AstraZeneca. I.J.D. declares advisory roles for Roche and Apexigen and consultant roles for Celgene, BMS, and Pfizer. A.O-T. reports advisory roles for Roche and Lilly. L.B.K. reports advisory role for Roche. All other authors report no conflicts of interest.

Authorship statement. Study conception and design: S.G., D.W.P., M.F., A.O-T., R.I.J., I.F.P. Data collection: S.G., A.B., M.F., S.P., A.M.A., N.J.R., I.F.P., L.B.K., A.P., G.W.R. Data analysis and interpretation: S.G., C.A.B., I.J.D., A.O-T., A.M.A., R.I.J., T.Y.P., I.F.P., A.P., Manuscript preparation: S.G., D.W.P., I.J.D., A.O-T., S.P., R.I.J., N.J.R., T.Y.P., I.F.P., L.B.K., G.W.R., Final approval of manuscript: All authors.

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