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Intracystic interferon-alpha in pediatric craniopharyngioma patients: an international multicenter assessment on behalf of SIOPE and ISPN

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Abstract

Background: Craniopharyngiomas are frequent hypothalamo-pituitary tumors in children, presenting predominantly as cystic lesions. Morbidity from conventional treatment has focused attention on intracystic drug delivery, hypothesized to cause fewer clinical consequences. However, the efficacy of intracystic therapy remains unclear. We report the retrospective experiences of several global centers using intracystic interferon-alpha.

Methods: European Société Internationale d'Oncologie Pédiatrique and International Society for Pediatric Neurosurgery centers were contacted to submit a datasheet capturing pediatric patients with cystic

craniopharyngiomas who had received intracystic interferon-alpha. Patient demographics, administration schedules, adverse events, and outcomes were obtained. Progression was clinical or radiological (cyst reaccumulation, novel cysts, or solid growth).

Results: Fifty-six children (median age, 6.3 y) from 21 international centers were identified. Median follow-up from diagnosis was 5.1 years (0.3–17.7 y). Lesions were cystic (n = 22; 39%) or cystic/solid (n = 34; 61%). Previous progression was treated in 43 (77%) patients before interferon use. In such cases, further progression was delayed by intracystic interferon compared with the preceding therapy for cystic lesions (P = 0.0005). Few significant attributable side effects were reported. Progression post interferon occurred in 42 patients (median 14 mo; 0–8 y), while the estimated median time to definitive therapy post interferon was 5.8 (1.8–9.7) years.

Conclusions: Intracystic interferon-alpha can delay disease progression and potentially offer a protracted time to definitive surgery or radiotherapy in pediatric cystic craniopharyngioma, yet demonstrates a favorable toxicity profile compared with other therapeutic modalities—important factors for this developing age group. A prospective, randomized international clinical trial assessment is warranted.

Key words

craniopharyngioma | intracystic interferon | pediatric | retrospective

Importance of the study

Despite advances in neurosurgery and radiotherapy, the management of childhood craniopharyngioma remains challenging because of ongoing posttreatment morbidity concerns. As such, scope remains for therapeutic innovation. The cystic composition of pediatric craniopharyngiomas makes them ideal candidates to evaluate one such development: the instillation of intracystic agents—designed to obtain durable cyst shrinkage with minimum consequent toxicity. This global, multicenter assessment represents the broadest clinical experience ever reported of one such intracystic agent: interferon-alpha. The study is the first to show a progression-free survival advantage for interferon-alpha in cystic craniopharyngiomas compared with established treatments and a delay to definitive surgery or radiotherapy for several years. Interferon-alpha also appears to have an improved toxicity profile compared with historical intracystic therapies, including bleomycin and radioisotopes. Consequently, the authors propose that this study provides foundation for a global, prospective randomized clinical trial of intracystic interferon in childhood craniopharyngioma, now under consideration.

Craniopharyngiomas represent one of the most frequently diagnosed hypothalamo-pituitary lesions in children.[1,2] Postulated to arise from embryonic remnants of Rathke's pouch during development of the fetal adenohypophysis,[3,4] craniopharyngiomas can consist of either cyst cavities lined by secretory squamous epithelium and/or solid components containing both keratin products and calcium.[5–8] In childhood, craniopharyngiomas are predominantly cystic in composition.[9]

Despite a benign histological classification, the most favorable management strategy for pediatric craniopharyngiomas continues to prove controversial as lesional intimacy with several critical structures in the developing brain can pose a significant risk to neurological, visual, endocrinological, and metabolic functioning.[10–13] Surgical resection is generally considered curative but is often associated with significant morbidity and mortality,[10,13,14] while recurrence post complete resection has also been reported.[12,14–16] Conformal radiotherapy is the standard adjuvant therapy used, but concerns regarding its use persist regarding neurocognitive, vascular, and endocrinological sequelae,[17,18] while the efficacy of systemic chemotherapy has proved disappointing.[19] Molecular profiling of these lesions suggests a role for novel targeted biological agents in the future,[20] yet such personalized therapy remains elusive.

Nevertheless, the recent management of pediatric cystic craniopharyngioma has shifted to focus on intralesional therapies, administered via an indwelling catheter with the objective of postponing or sparing the adverse effects of more conventional therapies with minimal clinical consequences for the patient. One such agent that is becoming increasingly favored via this route is interferon-alpha, on the premise that craniopharyngioma cyst walls share their cells of origin with squamous cell skin carcinomas, where interferon is a recognized antiproliferative and immunomodulatory therapy.[21–23] Institutional reports of intracystic interferon in craniopharyngioma appear promising, suggesting an acceptable side-effect profile and effectiveness at inducing tumor response.[6,24,25] However, conclusions on the efficacy of this therapy remain cautious, since analyzed cohorts were limited in size and the duration of any responses observed remain unpublished.

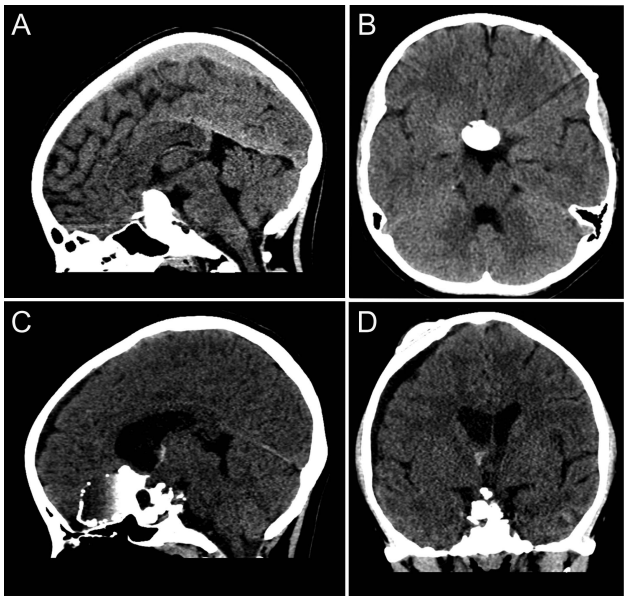
In an attempt to address this, we have performed an international, multicenter retrospective analysis of intracystic interferon use in pediatric craniopharyngioma among participating institutions within SIOPE (the European subgroup of the International Society of Pediatric Oncology) and ISPN (the International Society of Pediatric Neurosurgery). The efficacy of intracystic interferon in delaying or preventing both disease progression and the need for subsequent definitive surgery or radiotherapy were evaluated, along with toxicity and clinical outcomes following treatment.

Methods

Clinical leads for pediatric oncology and neurosurgery from member institutions of both SIOPE and ISPN were invited electronically to complete an anonymized datasheet for any patients aged below 18 years with a histologically proven or radiologically suspected craniopharyngioma that had received intracystic interferon-alpha therapy at any time point in that center. Patients with solid craniopharyngiomas, incompatible histological diagnoses, or age older than 18 years were excluded. Data were collected on patient demographics, presenting symptomatology, timings of all therapies, adherence to the Toronto protocol for intracystic interferon administration[9] (Fig. 1), intracystic dose scheduling, acute and long-term adverse effects of interferon therapy, and clinical outcomes. Toxicity of drug administration was graded as per the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE). The study received approval from the local research ethics boards of responding centers.

Lesional size was measured radiologically, irrespective of composition, according to the 2 largest diameters from axial, sagittal, and coronal MR images using fluid attenuation inversion recovery sequences and T1-weighted images (with and without contrast enhancement). A largest diameter threshold of 4 cm, in keeping with published literature,[26] was used to delineate large and small lesions for survival analysis comparisons as defined below.

Statistical analyses were performed using SPSS v22.0. Symptom interval was defined as the time elapsed from initial complaint to diagnostic scan. Comparison of parametric continuous variables was performed by independent sample *t*-testing with 95% confidence intervals. Survival analysis was performed by the Kaplan–Meier method with significance values for comparisons established by the log rank test. Progression-free survival (PFS) was defined in years from the date of tumor diagnosis to the date of further disease progression (clinical or radiological), death, or censorship if alive. Radiological progression encompassed cyst reaccumulation, novel cyst formation, or solid growth from the date of last intervention. Definitive therapy was defined as either surgical tumor resection or focal radiotherapy. Median follow-up was estimated by the inverse Kaplan–Meier method.[27] Significance was achieved with *P*-values below 0.05.



Intracystic Interferon Administration Schedule

Drug	Route	Dose	Weeks	Days
Interferon-alfa-2b (Intron A – ready to use solution) OR Interferon-alfa-2a	Intracystic injection	3,000,000 IU (volume 1 mL)	Weeks 1 – 4	Monday, Wednesday Friday

- 1 cycle = 4 weeks treatment (total dose per cycle = 36,000,000 IU)
- Cycle may be repeated depending on response.
- Before initiation of treatment a permeability study should have ruled out leakage of contrast and confirmed appropriate position of the tip of the ommaya catheter within the cyst. This permeability study is recommended to be performed 2 weeks after catheter placement or later.
- At the start of therapy (day 1) the maximum possible amount of cystic fluid should be removed before injection of interferon-alfa, taking the result of the permeability study (cyst volume) and patient comfort into account. A Normal Saline flush (1mL) should follow interferon alfa injection.
- For subsequent administrations in the cycle, cystic fluid aspirations for at least 1.5-2 mL should be performed, followed by 1 mL (3 million IU) interferon-alfa injection, followed by 1 mL flush of normal saline.

Fig. 1 CNS permeability studies revealing contrasting craniopharyngioma cyst wall integrity and the Toronto protocol for intracystic interferon-alpha administration. CNS permeability studies—a sagittal CT (A) and axial CT (B) of the brain post instillation of contrast through an Ommaya reservoir ruling out leakage. This is clearly distinct from a sagittal CT (C) and a coronal CT (D) of the brain post contrast instillation through an Ommaya reservoir demonstrating leakage of contrast through the cyst wall into the body of the right lateral ventricle and adjacent foramen of Monro. These images are alongside the administration schedule for intracystic interferon-alpha devised by the Hospital for Sick Children, Toronto. This is generally accepted as the global standard of care protocol.

Results

Demographics

Fifty-six patients from 21 responding SIOPE and ISPN centers fulfilled the inclusion criteria (Table 1, Supplementary Table S1). The median age of the cohort was 6.3 years (range 0.3–17 y) with a male:female ratio of 1.2:1. A histological diagnosis of adamantinomatous craniopharyngioma was made from lesional tissue for 37/56 (66%) patients. This was following an initial biopsy (n = 15) or definitive surgical resection (n = 22), either at diagnosis (n = 20) or following eventual surgical intervention (n = 2). In the 19 other remaining cases, diagnosis was radiological (based on tumor location, presence of calcification on CT imaging, etc) in combination with the presence of classical craniopharyngioma cyst fluid (documented intraoperatively as thick and oil-like and/or with the presence of cholesterol crystals on histology). Of the 20 children who underwent upfront definitive surgery, macroscopic tumor resection was achieved in 3 cases, while an incomplete resection or debulking was recorded for 17 cases. Almost 40% of the group (n = 22) appeared either purely or predominantly cystic on imaging, while two-thirds of children had radiological evidence of hypothalamic involvement.

Table 1 Clinical characteristics of the pediatric craniopharyngioma cohort

Patient Number	N = 56
Median age, y (range)	6.3 (0.3–17)
Median follow-up, y (range)	5.1 (0.3–17.7)
Median follow-up post IFN, y (range)	2.7 (0.1–10.2)
Sex	
Male	31 (55%)
Female	25 (45%)
Ethnicity	
Caucasian	31 (55%)
African	7 (13%)
East Asian	8 (14%)
Other	8 (14%)
Not recorded	2 (4%)
Hypothalamic involvement	
Yes	37 (66%)
No	19 (34%)
Histology subtype	
Adamantinomatous	37 (66%)
Not recorded	19 (34%)
Radiological appearance	
Cystic predominant	22 (39%)
Solid/cystic	34 (61%)
Status post IFN therapy	
Alive—no disease progression	14 (25%)
Alive—experienced disease progression	37 (66%)
Dead	5 (9%)
Survival	
10-year overall survival	91% (±6%)

IFN = intracystic interferon-alpha.

With respect to the timing of treatment initiation from diagnosis, 48 (86%) patients were treated either immediately or within days of diagnosis. For the remaining 8 children, therapy was initiated at a median of 2 months (range 1–6 mo) from diagnosis. Intracystic interferon therapy was the initial treatment for 13/56 (23%), with the remaining cohort having undergone preceding therapies, including cyst aspiration/fenestration, tumor excision, focal radiotherapy, and radioisotope therapy (Supplementary Table S2). Across the entire cohort, 29 (52%) patients underwent cyst aspiration or fenestration as part of prior therapy. This was performed as either a one-time procedure for 17 (59%) patients or multiple times for 12 (41%) children. Seventeen (30%) patients had been previously treated with radiotherapy, including conformal radiotherapy (n = 9), gamma knife radiosurgery (n = 5), and proton beam therapy (n = 3) (Supplementary Table S3). The median dose administered was 54 Gy (21.8–54 Gy), while the median time to progression following this treatment modality was 2 years (0.3–9 y). Of the 22 patients with predominantly cystic lesions, interferon was the primary therapy in 6 cases (27%), while preceding therapies included aspiration alone (n = 10; 45%), fenestration (n = 3; 14%), surgical resection (n = 2; 9%), and radiotherapy (n = 2; 9%).

Clinical Presentation

Across the cohort, the most common presenting features at diagnosis included raised intracranial pressure (37/56, 66%), pituitary endocrinopathies (25/56, 45%), impaired visual acuity (25/56, 45%), visual field cuts (18/56, 32%), behavioral difficulties (8/56, 14%), and cognitive decline (3/56, 5%). The median symptom interval was 3 months (0.3–48 mo).

Unsurprisingly, at the point of commencing intracystic interferon therapy, a higher proportion of patients had developed clinical anomalies compared with presentation. Raised intracranial pressure had been observed in 40/56 children (71%), while reduced visual acuity was recorded for 30/56 (54%), pituitary dysfunction in 27/56 (48%), visual field deficits in 20/56 (36%), behavioral problems in 10/56 (18%), and cognitive difficulties in 4/56 cases (7%).

Intracystic Interferon Therapy

Concordance with the Toronto protocol for intracystic interferon administration was generally observed, albeit not universally. Prior to commencing therapy, contrast-enhanced brain imaging to ensure cyst wall integrity was performed in 52/56 (93%) patients. Initial aspiration of the cyst was in accordance with the protocol for 46/56 (82%) children, while each intracystic interferon-alpha dose administered corresponded to 3 million international units across all centers. The median number of doses administered to a patient was 14 (range 6–84) due to several centers offering patients repeated cycles of therapy. However,

7 centers (13%) administered fewer than the standard 12 doses, constituting a typical cycle without an explanatory cause such as secondary toxicity or disease progression.

Treatment and Outcomes

At the point of last assessment (median follow-up 5.1 y [range 0.3–17.7 y]; median follow-up post interferon 2.7 y [0.1–10.2 y]), 51/56 (91%) patients remained alive, with 14 (25%) children demonstrating no evidence of disease progression. Five patients died within the follow-up period. Two patients died of ongoing disease progression, 1 died from an endocrinopathy-induced electrolyte imbalance, and 2 died from unrelated, unanticipated infections. All patients had received interferon as the last therapeutic option after repeated surgeries and focal radiation had failed.

In order to assess the comparative impact of intracystic interferon at delaying disease progression in craniopharyngioma, patients who had also received previous therapy were assessed (n = 43). One patient had incomplete PFS data, resulting in an evaluable cohort of 42 children. Across this group, interferon therapy appeared to delay disease progression compared with each child's corresponding previous treatment (estimated median time to progression = 0.8 y [95% CI: 0.3–1.3 y] vs 0.4 y [95% CI: 0.2–0.6 y], P = 0.022). When this cohort was categorized according to lesional composition, this delay in progression demonstrated that post interferon therapy was exclusively for children with predominantly cystic craniopharyngiomas (estimated median time to progression = 1.3 y [95% CI: 0.7–1.9 y] vs 0.3 y [95% CI: 0.2–0.39 y], P = 0.0005; Fig. 2A), and not for those with solid/cystic lesions (estimated median time to progression = 0.8 y [95% CI: 0.1–1.5 y] vs 0.6 y [95% CI: 0.1–1.1 y], P = 0.339; Fig. 2B). The predominantly cystic cohort trended toward a younger patient age than their solid/cystic counterparts (mean age 5.7 ± 1.1 y vs 7.9 ± 0.8 y, P = 0.1).

Disease progression (radiological or clinical) following intracystic interferon therapy was reported in 42/56 (75%) patients at a median time of 14 months (range 0–8 y; Table 2; Supplementary Figure S1). Neither large lesional size, radiological evidence of hypothalamic infiltration, nor clinical hydrocephalus at presentation impacted significantly on time to progression following interferon administration. Radiological progression due to the development of new cysts or solid tumor growth was observed more frequently than the reaccumulation of previously treated cysts. At the time of last assessment, 14/42 (33%) patients had not undergone definitive surgery or radiotherapy for their progressive disease, instead receiving further courses of intracystic interferon therapy or embarking on periods of clinical surveillance. Of the 24/42 (57%) children who had undergone radical surgery or radiotherapy for disease progression, the median time to such treatment was 5.8 years (1.8–9.7 y). It was not possible to assess the impact of intracystic interferon, before and after use, on time to definitive therapy due to the insufficient numbers of appropriate patients.

Tolerability and Adverse Events

The administration of intracystic interferon was generally well tolerated across the cohort, with 23/56 (41%) children

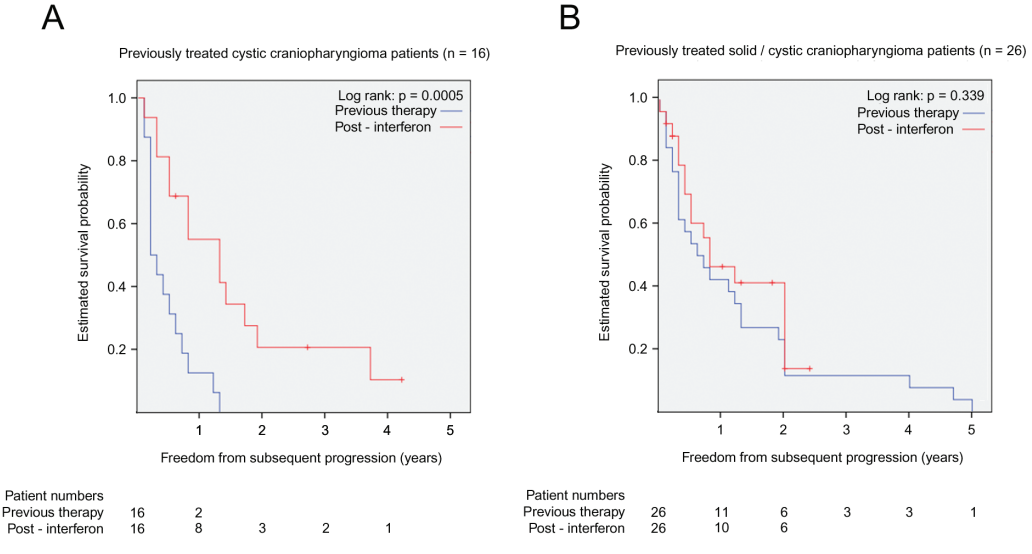


Fig. 2 Time to disease progression for intracystic interferon-alpha therapy compared with the patient's preceding therapy in children with predominantly cystic and solid/cystic craniopharyngiomas. Forty-three of 44 patients had previously been treated for disease progression prior to interferon use. For these patients, time to disease progression post interferon therapy was compared with each patient's corresponding prior therapy. Kaplan–Meier curves demonstrated a significant delay in disease progression post interferon therapy (red line) compared with the previous therapy (blue line) for (A) children with predominantly cystic craniopharyngiomas (n = 16, P = 0.0005), but not for (B) those with solid/cystic lesions (n = 26, P = 0.339).

experiencing no adverse effects during or following therapy. The most common adverse effects included influenza-like malaise ($n = 16$; 29%), headaches ($n = 10$; 18%), fatigue ($n = 7$; 13%), transient hyponatremia ($n = 1$; 2%), appetite loss ($n = 1$; 2%), and weight loss ($n = 1$; 2%). These symptoms were typically grades 1–2 in severity and resolved within days or a short number of weeks without long-standing sequelae.

No toxic deaths attributable to the drug were reported. Nevertheless, 2 cases of suspected significant adverse events were observed. The first case involved a 15-year-old male, previously managed using cyst fenestration and ventriculo-peritoneal shunt insertion for a cystic craniopharyngioma causing raised intracranial pressure, who was treated with intracystic interferon therapy for cystic reaccumulation. After a standard cycle of 12 doses of interferon treatment, the patient developed worsening headaches and acute visual deterioration in his left eye, which was accompanied by evidence of increased cyst wall contrast enhancement and surrounding, extrinsic, localized edema on MR brain imaging. Visual and radiological improvement was observed following a 3-month course of systemic steroid therapy. The treating center postulated that the patient's deterioration may have reflected drug extravasation beyond the cyst during the treatment cycle.

The second case involved an 8-year-old boy re-presenting with radiological recurrence of a solid/cystic lesion who had previously been treated as an infant with debulking surgeries and focal radiotherapy. Pretreatment cyst wall permeability imaging revealed contrast leakage, but treatment continued as literature has suggested toxicity from interferon extravasation is innocuous. During the first cycle of therapy the patient suffered extreme fatigue, while 2 weeks following completion of a standard treatment cycle, he developed extreme confusion, incontinence, and hypernatremia. Imaging at this time revealed worsening hydrocephalus and widespread diffuse brain atrophy, albeit with a stable suprasellar mass. The patient improved neurologically following cerebrospinal fluid (CSF) diversion therapy, but diffuse atrophy persisted on subsequent imaging such that further courses of interferon therapy were abandoned.

Table 2 Progression and treatment data for craniopharyngioma patients who progressed post intracystic interferon-alpha therapy

Patients Progressed after IFN	$N = 42$
Initial radiological appearance	
Cystic	18 (43%)
Solid/cystic	24 (57%)
Therapy prior to IFN	
Nil (IFN first therapy)	11 (26%)
Aspiration/cyst fenestration only	15 (36%)
Resection + RT	7 (16%)
Aspiration/cyst fenestration + RT	3 (7%)
Resection only	2 (5%)
Resection + aspiration	2 (5%)
Resection + RT + aspiration	1 (2%)
Radioisotope + RT + aspiration	1 (2%)
Type of progression	
Cyst reaccumulation	10 (24%)
New cyst(s)	12 (29%)
Solid growth	7 (16%)
Clinical progression	3 (7%)
Combination (new cyst[s]/solid/clinical)	10 (24%)
Subsequent therapy	
Surgery	11 (26%)
IFN rechallenge	6 (14%)
Surgery + RT	5 (12%)
RT	5 (12%)
IFN rechallenge then surgery	2 (5%)
IFN rechallenge then surgery +RT	1 (2%)
IFN to new cysts	2 (5%)
Observation/no intervention	6 (14%)
Not documented	4 (10%)

Abbreviations: IFN = intracystic interferon-alpha; RT = radiotherapy.

Posttreatment Clinical Outcomes

The effect of intracystic interferon therapy on the most common clinical deficits identified prior to commencing treatment was monitored across the cohort (Fig. 3). Of the 43 patients who had undergone preceding therapy, 25 (58%) developed new clinical deficits between this preceding therapy and the commencement of interferon therapy. Clinical evaluations performed at interferon treatment completion revealed that the vast majority of patients previously suffering from raised intracranial pressure (39/40; 98%), visual acuity decline (27/30; 90%), visual field cuts (18/20; 90%), pituitary dysfunction (26/27; 96%), behavioral difficulties (10/10; 100%), or cognitive deterioration (3/4; 75%) had either stabilized or improved following intracystic interferon therapy alone, thereby suggesting that this treatment could potentially delay or occasionally reverse clinical deterioration in almost all of the patients who receive it.

Discussion

This global, retrospective analysis of intracystic interferon-alpha therapy in pediatric craniopharyngioma is the first to show a PFS advantage for interferon in children with cystic lesions compared with other established treatments. The study also demonstrates that intracystic interferon therapy may have the potential to delay definitive treatments such as radical surgery or intracranial radiotherapy by several years—a critical benefit for the developing brain, which has a well-established vulnerability to the acute and long-term deleterious effects of such conventional treatment modalities.[10,13,14,17,18] Finally, analyzing a cohort with one of the longer follow-up periods published to date, we have demonstrated that intracystic interferon appears to stabilize or occasionally reverse clinical deterioration in treated patients with a toxicity profile that is favorable compared with alternative intracystic therapies.[9]

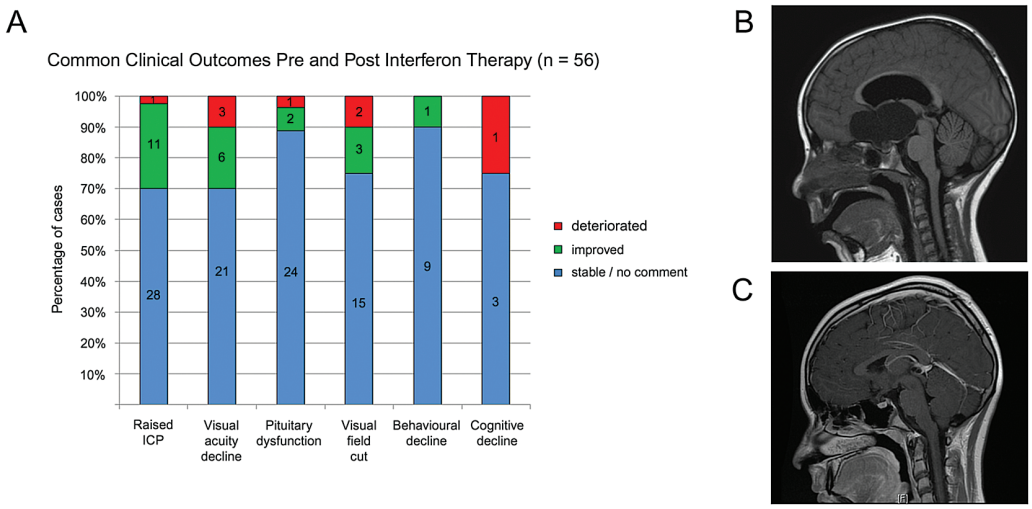


Fig. 3 Clinical outcomes post intracystic interferon therapy. (A) The subsequent clinical outcomes following intracystic interferon therapy for patients demonstrating raised intracranial pressure, visual deficits, pituitary dysfunction, behavioral difficulties, or cognitive decline at the point of commencing treatment. Improvements are colored green; stability, blue; and ongoing decline, red. The graph suggests that intracystic interferon therapy can delay ongoing clinical progression for the vast majority of patients who receive it. (B, C) Highlight of one of the most sustained clinical responses to intracystic interferon therapy across the patient cohort. (B) Presentation scan of the female patient aged 4 years, when she was subsequently diagnosed with a cystic craniopharyngioma. The patient was treated with 2 cycles of intracystic interferon-alpha. (C) The patient continues to demonstrate a sustained complete response. She is now aged 11 years; 7 years post diagnosis. No further treatment has been required. Clinically the patient has normal visual acuity and fields, and other than precocious puberty diagnosed at the age of 8 years, intact pituitary function.

Interferon-alpha belongs to the interferon cell signaling family of proteins that are produced following pathogenic induction from agents including bacteria, viruses, and neoplasms.[28] While their precise mechanism of action in tumor cells remains elusive, interferons are postulated to be implicated in the generation of an immunological response via immune cell activation, cytokine induction, and inhibition of neoplastic vascularization.[29] Alternatively, interferons may cause direct promotion of cellular differentiation and inhibition of proliferation by modulating signaling mechanisms, including the pathways of phosphatidylinositol-3 kinase and Janus kinase/signal transducers and activators of transcription.[30,31] Based on these hypotheses, interferon therapy has been used for a range of hematological and solid cancers.[22,32–36] Such cellular mechanisms have been reported in pediatric cystic craniopharyngioma studies with evidence of both increased Fas-induced cell apoptosis and reduced immunomodulating alpha-definsin concentrations in cyst fluid following interferon-alpha instillation.[1,6]

While repeated cyst aspiration via an implanted reservoir has been championed as the simplest and safest option currently available to patients with cystic craniopharyngiomas,[37] this study demonstrates that the intratumoral instillation of interferon appears superior to regular cyst aspiration in delaying reaccumulation and progression. This intralesional therapeutic approach would also potentially benefit the patient with respect to protracted disease control and reduced hospital attendances while improving the utilization of resources for the treating clinician.

The results of this analysis also build on preceding reports of potential efficacy and safety with intracystic interferon therapy use in pediatric craniopharyngioma.[6,9,24,25] The largest of these was a prospective study of 60 children treated across 3 international centers in the period 2000–2009.[25] Thirty-nine patients (65%) received intracystic interferon-alpha as primary treatment, while the remaining children had already undergone either unsuccessful surgery or intracystic bleomycin therapy. The majority of patients (78%) attained more than 50% cyst shrinkage with therapy. While data on disease progression was limited, 13 children (22%) had progressed at a mean follow-up period of 3.7 years and underwent subsequent surgical intervention. Similar to our study, the most frequent side effects observed were mild and transient, and included headaches, palpebral edema, fatigue, and arthralgia. None of these sequelae required discontinuation of therapy and no mortalities were reported. One patient suffered visual decline despite cyst shrinkage, while 8 children developed new endocrinopathies.

This study demonstrated that intracystic interferon therapy has a therapeutic benefit in purely or predominantly cystic craniopharyngiomas, yet failed to delay disease progression in lesions comprising a significant solid component. This reflects the observations of groups using this and other intracystic therapies[9,38–42] and implies the ongoing need for novel therapies for such solid craniopharyngiomas. In addition, while certain centers advocated retreatment of progressive disease with several cycles of interferon, particularly in the face of cystic reaccumulation, this was not a universal practice, suggesting that

awareness regarding the ability to repeatedly administer interferon for cystic recurrence is lacking.

Due to limited numbers of appropriate cases, the current study was unable to clearly establish whether intracystic interferon therapy delayed only cystic reaccumulation, as opposed to the development of new cysts or the evolution of solid tissue growth. This may explain why only 2/12 children with new cyst progressive disease underwent reservoir reimplantation and subsequent interferon therapy to these new cysts. Future sizable, clinical trials will help to evaluate this. However, given current knowledge of intracystic interferon toxicity compared with conventional alternatives, such a strategy for new cyst progression seems warranted if feasible. Randomized prospective clinical trials should also help define criteria to define tumor response and address other logistical limitations of this study, including its retrospective nature, the lack of central histological review at diagnosis and central radiological review of initial and follow-up imaging, together with the inconsistent adherence of centers to standardized treatment protocols. Such a study would also allow for a sustained, protracted period of follow-up to assess true impact on visual, endocrine, and cognitive functioning. It is hoped that such future trial work would also contribute samples to ongoing research in craniopharyngioma origin and development, including a focus on pro-inflammatory markers found within cyst fluid,[1] their value as surrogate markers of disease activity, and the subsequent influence on these markers by interferon therapy. In turn, this may further elucidate our understanding of interferon efficacy and tumor response.

Unlike intracystic administration of bleomycin or radioisotopes,[9] the toxicity profile of intralesional interferon-alpha generated from this analysis is comparatively favorable, with almost half of treated children experiencing no side effects, and the majority of side effects being transient and low grade in severity. Furthermore, no toxic deaths were reported. This echoes the general findings from the other craniopharyngioma studies of intracystic interferon-alpha.[6,9,24,25]

Higher-grade toxicity was observed in 2 patients from the current cohort. In both cases, the likely cause was drug leakage into surrounding CSF spaces. In one case, the pretreatment cyst wall permeability study had identified a rupture, but treatment was continued because of interferon's apparent safety profile from literature on its intrathecal administration.[43,44] The second patient deteriorated with ongoing therapy after initial imaging had revealed an intact cyst wall. However, the initial and cumulative cyst volumes aspirated from this patient are unclear, and the child developed worsening severe headache after several doses had been administered, a clinical sign suggestive of either drug leakage or cyst wall hemorrhage which can occur with vigorous cyst drainage.

Although not observed in the larger cohort analyses, similar case reports of significant toxicity following intracystic interferon-alpha administration in craniopharyngioma are now emerging, secondary to drug extravasation into CSF spaces.[45,46] In one report, a craniopharyngioma patient suffered a focal neurological event, with subsequent permeability imaging revealing suspected cyst rupture,[45] while another described a 13-year-old patient with recurrent, cystic craniopharyngioma who developed permanent visual field loss and reversible acuity decline following the concomitant administration of intracystic and subcutaneous pegylated interferon-alpha.[46] Retrospective permeability imaging revealed a cyst wall leak.

Such results reinforce the importance of performing a permeability imaging study before and, if required, during intracystic therapy and acting on the results obtained. Despite interferon being used as a safe intrathecal agent in other contexts, its evaluation as an intratumoral agent in craniopharyngioma remains a work in progress. In this regard, when radiological evidence of cyst wall permeability is encountered, it is the authors' recommendation that ongoing treatment with interferon should not proceed. This stance should remain until several outstanding aspects of intracystic interferon use are elucidated from further clinical trial work in craniopharyngioma, such as the most suitable drug formulation and schedule, whether previous therapy influences the likelihood of treatment failure or success, and whether lesional or patient subgroups gain benefit compared with others.[47] Until then, decisions regarding suitable candidates for intracystic interferon therapy should remain within the confines of a craniopharyngioma multidisciplinary team setting, with a stipulation that all proposed patients undergo cyst wall permeability screening as required with treatment suspension if extravasation is encountered at any point.

In summary, findings from this retrospective analysis and other literature suggests that interferon-alpha holds promise as an intracystic therapy for craniopharyngioma, at the very least for a subset of patients with cystic lesions, with evidence of improved PFS and sustained tumor responses in conjunction with fewer episodes of significant morbidity to date than its predecessors, β-emitting radionucleotides and bleomycin. Interferon therapy can defer definitive surgery or radiotherapy for several years, thereby protecting the developing brain from the deleterious consequences of such conventional treatments. A multinational, global, randomized controlled analysis is now warranted to truly evaluate interferon efficacy versus matched aspiration frequency alone in this setting, in addition to defining the appropriate patients, sustainability of response, drug effect on neighboring cysts or solid craniopharyngioma components if present, and precise toxicity profile from administering interferon by this route. Such prospective multinational clinical trial work is imperative to enhance patient outcome and quality of life while the development of targeted molecular therapies has yet to evolve for this tumor group.

Supplementary Material

Supplementary material is available at *Neuro-Oncology* online.

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References

1. Pettorini BL, Inzitari R, Massimi L, et al. The role of inflammation in the genesis of the cystic component of craniopharyngiomas. *Childs Nerv Syst*. 2010;26(12):1779–1784.
2. Jane JA Jr, Laws ER. Craniopharyngioma. *Pituitary*. 2006;9(4):323–326.
3. Merchant TE, Kiehna EN, Sanford RA, et al. Craniopharyngioma: the St. Jude Children's Research Hospital experience 1984–2001. *Int J Radiat Oncol Biol Phys*. 2002;53(3):533–542.
4. Garrè ML, Cama A. Craniopharyngioma: modern concepts in pathogenesis and treatment. *Curr Opin Pediatr*. 2007;19(4):471–479.
5. Alén JF, Boto GR, Lagares A, de la Lama A, Gómez PA, Lobato RD. Intratumoural bleomycin as a treatment for recurrent cystic craniopharyngioma. Case report and review of the literature. *Neurocirugia (Astur)*. 2002;13(6):479–485; discussion 485.
6. Ierardi DF, Fernandes MJ, Silva IR, et al. Apoptosis in alpha interferon (IFN-alpha) intratumoral chemotherapy for cystic craniopharyngiomas. *Childs Nerv Syst*. 2007;23(9):1041–1046.
7. Ingraham FD, Scott HW Jr. Craniopharyngiomas in children. *J Pediatr*. 1946;29:95–116.
8. Kramer S, Mckissock W, Concannon JP. Craniopharyngiomas. Treatment by combined surgery and radiation therapy. *J Neurosurg*. 1961;18:217–226.
9. Bartels U, Laperriere N, Bouffet E, Drake J. Intracystic therapies for cystic craniopharyngioma in childhood. *Front Endocrinol (Lausanne)*. 2012;3:39.
10. Müller HL. Childhood craniopharyngioma: current controversies on management in diagnostics, treatment and follow-up. *Expert Rev Neurother*. 2010;10(4):515–524.
11. Srinivasan S, Ogle GD, Garnett SP, Briody JN, Lee JW, Cowell CT. Features of the metabolic syndrome after childhood craniopharyngioma. *J Clin Endocrinol Metab*. 2004;89(1):81–86.
12. Villani RM, Tomei G, Bello L, et al. Long-term results of treatment for craniopharyngioma in children. *Childs Nerv Syst*. 1997;13(7):397–405.
13. Kalapurakal JA, Goldman S, Hsieh YC, Tomita T, Marymont MH. Clinical outcome in children with craniopharyngioma treated with primary surgery and radiotherapy deferred until relapse. *Med Pediatr Oncol*. 2003;40(4):214–218.
14. Steinbok P, Hukin J. Intracystic treatments for craniopharyngioma. *Neurosurg Focus*. 2010;28(4):E13.
15. Duff J, Meyer FB, Ilstrup DM, Laws ER Jr, Schleck CD, Scheithauer BW. Long-term outcomes for surgically resected craniopharyngiomas. *Neurosurgery*. 2000;46(2):291–302; discussion 302.
16. Fahlbusch R, Honegger J, Paulus W, Huk W, Buchfelder M. Surgical treatment of craniopharyngiomas: experience with 168 patients. *J Neurosurg*. 1999;90(2):237–250.
17. Merchant TE, Kiehna EN, Kun LE, et al. Phase II trial of conformal radiation therapy for pediatric patients with craniopharyngioma and correlation of surgical factors and radiation dosimetry with change in cognitive function. *J Neurosurg*. 2006;104(2 Suppl):94–102.
18. Kiehna EN, Merchant TE. Radiation therapy for pediatric craniopharyngioma. *Neurosurg Focus*. 2010;28(4):E10.
19. Hargrave DR. Does chemotherapy have a role in the management of craniopharyngioma? *J Pediatr Endocrinol Metab*. 2006;19 Suppl 1:407–412.
20. Hölsken A, Sill M, Merkle J, et al. Adamantinomatous and papillary craniopharyngiomas are characterized by distinct epigenomic as well as mutational and transcriptomic profiles. *Acta Neuropathol Commun*. 2016;4:20.
21. Kim KH, Yavel RM, Gross VL, Brody N. Intralesional interferon alpha-2b in the treatment of basal cell carcinoma and squamous cell carcinoma: revisited. *Dermatol Surg*. 2004;30(1):116–120.
22. Edwards L, Berman B, Rapini RP, et al. Treatment of cutaneous squamous cell carcinomas by intralesional interferon alfa-2b therapy. *Arch Dermatol*. 1992;128(11):1486–1489.
23. Shin DM, Khuri FR, Murphy B, et al. Combined interferon-alfa, 13-cis-retinoic acid, and alpha-tocopherol in locally advanced head and neck squamous cell carcinoma: novel bioadjuvant phase II trial. *J Clin Oncol*. 2001;19(12):3010–3017.
24. Cavalheiro S, Dastoli PA, Silva NS, Toledo S, Lederman H, da Silva MC. Use of interferon alpha in intratumoral chemotherapy for cystic craniopharyngioma. *Childs Nerv Syst*. 2005;21(8–9):719–724.
25. Cavalheiro S, Di Rocco C, Valenzuela S, et al. Craniopharyngiomas: intratumoral chemotherapy with interferon-alpha: a multicenter preliminary study with 60 cases. *Neurosurg Focus*. 2010;28(4):E12.
26. Mallucci C, Pizer B, Blair J, et al. Management of craniopharyngioma: the Liverpool experience following the introduction of the CCLG guidelines. Introducing a new risk assessment grading system. *Childs Nerv Syst*. 2012;28(8):1181–1192.
27. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. *Control Clin Trials*. 1996;17(4):343–346.
28. Le Page C, Génin P, Baines MG, Hiscott J. Interferon activation and innate immunity. *Rev Immunogenet*. 2000;2(3):374–386.
29. Ferrantini M, Capone I, Belardelli F. Interferon-alpha and cancer: mechanisms of action and new perspectives of clinical use. *Biochimie*. 2007;89(6–7):884–893.
30. Stark GR, Kerr IM, Williams BR, Silverman RH, Schreiber RD. How cells respond to interferons. *Annu Rev Biochem*. 1998;67:227–264.
31. Platanias LC. Mechanisms of type-I- and type-II-interferon-mediated signalling. *Nat Rev Immunol*. 2005;5(5):375–386.
32. Ahmed S, Rai KR. Interferon in the treatment of hairy-cell leukemia. *Best Pract Res Clin Haematol*. 2003;16(1):69–81.
33. Strander H. Interferon treatment of human neoplasia. *Adv Cancer Res*. 1986;46:1–265.
34. Goldstein D, Laszlo J. The role of interferon in cancer therapy: a current perspective. *CA Cancer J Clin*. 1988;38(5):258–277.
35. Kirkwood JM, Ibrahim JG, Sosman JA, et al. High-dose interferon alfa-2b significantly prolongs relapse-free and overall survival compared with the GM2-KLH/QS-21 vaccine in patients with resected stage IIB-III melanoma: results of intergroup trial E1694/S9512/C509801. *J Clin Oncol*. 2001;19(9):2370–2380.
36. Salles G, Mounier N, de Guibert S, et al. Rituximab combined with chemotherapy and interferon in follicular lymphoma patients: results of the GELA-GOELAMS FL2000 study. *Blood*. 2008;112(13):4824–4831.
37. Moussa AH, Kerasha AA, Mahmoud ME. Surprising outcome of ommaya reservoir in treating cystic craniopharyngioma: a retrospective study. *Br J Neurosurg*. 2013;27(3):370–373.
38. Albright AL, Hadjipanayis CG, Lunsford LD, Kondziolka D, Pollack IF, Adelson PD. Individualized treatment of pediatric craniopharyngiomas. *Childs Nerv Syst*. 2005;21(8–9):649–654.
39. Barriger RB, Chang A, Lo SS, et al. Phosphorus-32 therapy for cystic craniopharyngiomas. *Radiother Oncol*. 2011;98(2):207–212.
40. Hasegawa T, Kondziolka D, Hadjipanayis CG, Lunsford LD. Management of cystic craniopharyngiomas with phosphorus-32 intracavitary irradiation. *Neurosurgery*. 2004;54(4):813–820; discussion 820.
41. Kickingereder P, Maarouf M, El Majdoub F, et al. Intracavitary brachytherapy using stereotactically applied phosphorus-32 colloid for

treatment of cystic craniopharyngiomas in 53 patients. *J Neurooncol*. 2012;109(2):365–374.

42. Voges J, Sturm V, Lehrke R, Treuer H, Gauss C, Berthold F. Cystic craniopharyngioma: long-term results after intracavitary irradiation with stereotactically applied colloidal beta-emitting radioactive sources. *Neurosurgery*. 1997;40(2):263–269; discussion 269.
43. Chamberlain MC. A phase II trial of intra-cerebrospinal fluid alpha interferon in the treatment of neoplastic meningitis. *Cancer*. 2002;94(10):2675–2680.
44. Gascon GG; International Consortium on Subacute Sclerosing Panencephalitis. Randomized treatment study of inosiplex versus combined inosiplex and intraventricular interferon-alpha in subacute sclerosing panencephalitis (SSPE): international multicenter study. *J Child Neurol*. 2003;18(12):819–827.
45. Sharma J, Bonfield CM, Singhal A, Hukin J, Steinbok P. Intracystic interferon-α treatment leads to neurotoxicity in craniopharyngioma: case report. *J Neurosurg Pediatr*. 2015;16(3):301–304.
46. Tiedemann LM, Manley P, Smith ER, Dagi LR. Visual field loss in a case of recurrent cystic craniopharyngioma during concomitant treatment with pegylated interferon α-2b. *J Pediatr Hematol Oncol*. 2016;38(1):e26–e28.
47. Bailey S, Parkes J. Intracystic interferon therapy in childhood craniopharyngioma: who, when and how? *Clin Endocrinol (Oxf)*. 2015;82(1):29–34.