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Cystic craniopharyngioma

Intratumoral chemotherapy with alpha interferon

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ABSTRACT

Objective: To assess whether the cystic craniopharyngiomas can be controlled with the use of intratumoral applications of interferon alpha. **Method:** Nineteen patients with the diagnosis of cystic craniopharyngioma were treated with intratumoral chemotherapy with interferon alpha from January 2002 to April 2006. All patients underwent placement of an intracystic catheter connected to an Ommaya reservoir. Through this reservoir were made applications during chemotherapy cycles. Each cycle corresponded to application of 3,000,000 units of interferon alpha three times per week on alternate days totalizing 36,000,000 units. Response to treatment was evaluated by calculating the tumor volume on MRI control after one, three and six months after the end of each cycle. Patients who developed worsening of symptoms or who had insignificant reduction in tumor volume during follow-up underwent repeat cycle chemotherapy. **Results:** Four patients received four cycles of chemotherapy, three patients received three cycles, six patients received two cycles and six patients received one. The lower percentage of reduction in tumor volume was 60% and the bigger reduction was 98.37%. Eleven patients had a reduction greater than 90%. Five patients had a tumor reduction between 75 and 90% and in three patients the tumors were reduced by less than 75%. No deaths occurred during treatment and side effects of interferon alpha were well tolerated. No treatment was discontinued. Follow-up after the last application ranged from one year and five months to three years and nine months. **Conclusion:** The intratumoral chemotherapy with interferon alpha decreases the volume of cystic craniopharyngiomas and so far can be considered a new therapeutic alternative.

Key words: cystic craniopharyngioma, interferon alpha, intratumoral chemotherapy, bleomycin, Ommaya reservoir.

Craniofaringioma cístico: quimioterapia intratumoral com interferon alfa

RESUMO

Objetivo: Avaliar se os craniofaringiomas císticos podem ser controlados com aplicações intratumorais de interferon alfa. **Método:** De janeiro de 2002 a abril de 2006, 19 pacientes foram submetidos à colocação de um cateter intracístico conectado a reservatório de Ommaya para aplicações intratumorais de ciclos de 36.000.000 de unidades de interferon alfa. A resposta ao tratamento foi avaliada pelo cálculo do volume tumoral na ressonância magnética de controle ao término de cada ciclo. **Resultados:** Os pacientes receberam de um a quatro ciclos de quimioterapia. Onze pacientes apresentaram uma redução do volume tumoral maior que 90%; cinco pacientes apresentaram uma redução entre 75% e 90% e três pacientes uma redução menor de 75%. Não houve óbitos durante o tratamento e os efeitos colaterais do inferferon alfa foram bem tolerados. Nenhum

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tratamento foi interrompido. **Conclusão:** A quimioterapia intratumoral com interferon alfa diminui o volume dos craniofaringeomas csticos e pode ser considerada uma nova alternativa terapêutica.

Palavras-chave: craniofaringioma cístico, interferon alfa, quimioterapia intratumoral, bleomicina, reservatório de Ommaya.

Craniopharyngiomas account for 1.2% to 4% of all brain tumors and 6 to 9% of all childhood tumors[1]. They are the most common non-glial tumors in childhood[2] and originate from the embryonic remains of squamous cells through the hypophyseal-pharyngeal duct.

Complete resection is often impossible without significant morbidity due to the proximity of the tumor to important brain structures, such as the optic chiasm, third cranial nerve, hypothalamus and internal carotid artery, which constitute obstacles during surgical manipulation. The mortality rate ranges from 11 to 42%. Even after complete macroscopic resection, the craniopharyngioma recurrence rate ranges from 23 to 50%[3].

Permanent harmful effects on behavior, learning and endocrine function after surgery with or without subsequent radiotherapy are common and may be devastating. There are frequent fluctuations in sodium level in the postoperative period such that patients at times exhibit diabetes insipidus and at other times inappropriate secretion of antidiuretic hormone, progressing with either hypernatremia or hyponatremia that is difficult to control and may lead to severe brain damage or even death. Patients may also exhibit hyperphagia, obesity, low stature and psychiatric disorders in the later postoperative period[1,2,4].

There is no consensus in the literature on the best way to treat an adamantinomatous craniopharyngioma in childhood. Intratumoral chemotherapy with bleomycin or the intracystic application of radiopharmacological agents may control these tumors, but numerous side effects have been described[5].

The aim of the present study was to determine whether the intracystic use of alpha interferon reduces and/or controls the volume of these craniopharyngiomas and whether this chemotherapy may be considered a novel treatment alternative.

METHOD

The research project and consent form were analyzed and approved by the Ethics Committee of the university hospital of the Universidade Federal de São Paulo/Escola Paulista de Medicina (São Paulo, Brazil).

Between January 2002 and April 2006, 19 patients diagnosed with cystic craniopharyngioma were treated with intratumoral chemotherapy with alpha interferon at the Neurooncology Unit of the Pediatric Oncology Institute of the Universidade Federal de São Paulo. Sixteen patients were male and three were female. Mean age was 11 years (minimum=one year 10 months; maximum=19 years).

Predominantly cystic craniopharyngiomas were considered those in which the cystic portion accounted for at least 60% of the tumor. This diagnosis was made using computed tomography and/or magnetic resonance imaging (MRI) of the cranium.

In the initial clinical condition, seven patients complained of headaches, three had vision loss, seven had low stature and two exhibited signs and symptoms of severe intracranial hypertension. Fourteen patients had not undergone any past treatment and five had been submitted to surgical resection, followed by recurrence of the tumor.

All patients underwent the implantation of an intratumoral silicone catheter connected to an Ommaya reservoir (HP®) and attached in the subgaleal space. Fifteen patients underwent frontal craniotomy for subfrontal, microsurgical access to the cyst. Three patients with nonhypertensive hydrocephalia underwent fenestration of the cyst and the placement of the catheter through neuroendoscopy. In one patient with an extensive cystic tumor measuring 7.7×5.6×6 cm^3 and compromising the entire right frontal lobe, the catheter was installed by direct puncture through an orifice in the right frontal trepanation (Fig 1A).

Tumor volume was calculated in the preoperative period as well as at one and six months following the end of treatment with RMI, using the measurements of the three largest axes. This value was multiplied by a correction factor of 0.52 due to the elliptical shape[6].

Fifteen days after surgery was considered the ideal time to begin the applications. The administration of alpha interferon was performed in a clinic setting under rigorous antisepsis three times a week on alternating days for one month (12 applications). One hour prior to each procedure, an anesthetic pomade (Enla®) was applied to the scalp above the Ommaya reservoir. Each application consisted of an injection of 3,000,000 units of alpha interferon, totaling 36,000,000 units, which was considered one treatment cycle.

After antisepsis, the puncture of the reservoir was performed with slow, delicate aspiration of the intracystic fluid. The volume to be aspirated prior to the injection of the drug was determined by the moment at which the patient began to complain of a headache of moderate in-

tensity, thereby avoiding the complete emptying of the cyst. One milliliter (ml) was the total volume of interferon injected. In order to achieve an adequate mixture of the drug and tumor fluid, further aspiration and re-injection of the drug/fluid mixture was performed slowly three times.

Control MRI of the cranium was performed at one, three and six months following the end of each cycle. Patients who demonstrated an important reduction in tumor size in these first six months continued to undergo MRI control every six months. Patients who progressed with a worsening of symptoms or either an increase or insignificant reduction in tumor size underwent an additional treatment cycle, repeating the same sequence of intervals in the control imaging exam.

RESULTS

The number of cycles to which each patient was submitted varied in accordance to the response of the craniopharyngioma to chemotherapy with alpha interferon (Table 1). The Kruskall-Wallis test was used to determine whether the number of cycles affected the tumor response, revealing no statistically significant difference in the reduction of tumor volume between cycles. The minimal interval between cycles was one month and the maximal interval was two year five months (mean= 6.12 months).

The follow-up period after the last application ranged from one year five months to three years nine months (mean=22 months). The total follow-up period from the placement of the catheter until June 2007 ranged from one year six months to five years (mean=3 years).

Table 2 displays the pretreatment and post-treatment tumor volume. The non-parametric Wilcoxon test for two non-independent samples was used to determine differences between initial and final volume measurements and revealed a statistically significant reduction in tumor volume (p=0.000). Figures 1A-B and 2A-2B display examples of control images taken during diagnosis and six months after the end of treatment.

During treatment, no patient progressed with a severe clinical aggravation that would indicate the interruption of the treatment or the use of conventional surgical treatment. Only one patient experienced greater vision impairment during treatment, which improved af-

Table 1. Number of cycles. Mean reduction in tumor volume and statistical result.

Total number of cycles	Number of patients	Tumor reduction (%)	Kruskal-Wallis test
1	6	87.15	
2	6	92.16	χ^2_{calc}=2.053
3	3	83.51	
4	4	86.13	

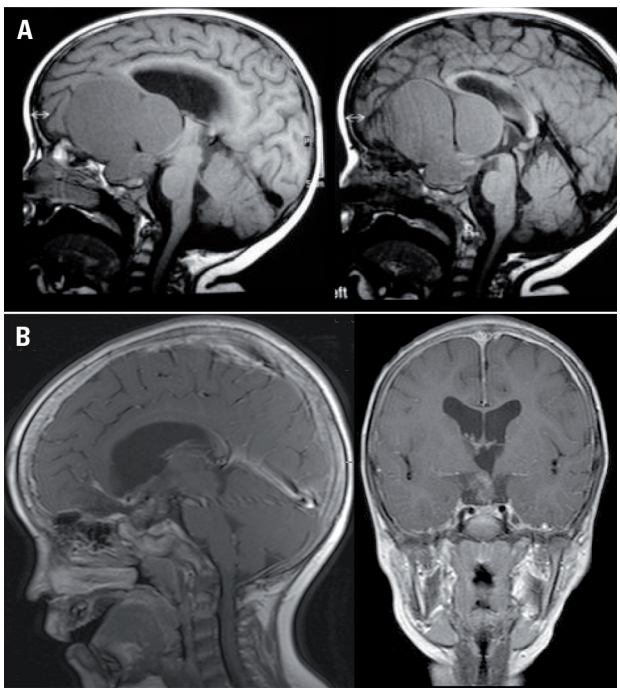

Fig 1. [A] Case 16: Craniopharyngioma with a large cystic component time of diagnosis; [B] Case 16: Two year follow-up after the last chemotherapy cycle.

Table 2. Tumor volume at diagnosis and six months after last treatment cycle and individual percentage of cyst reduction.

Patient	Initial size (cm^3)	Final size (cm^3)	Reduction (%)
1	23.29	2.98	87.20
2	54.08	4.69	91.32
3	35.04	0.81	97.68
4	37.44	2.63	92.97
5	12.87	1.71	86.71
6	7.02	2.08	70.37
7	39.0	15.6	60.0
8	3.36	0.14	95.83
9	9.79	0.94	90.39
10	34.94	1.06	96.96
11	40.32	4.65	88.46
12	52.32	3.57	93.17
13	25.74	4.8	81.35
14	23.29	3.37	85.53
15	16.38	1.06	93.52
16	134.53	2.18	98.37
17	7.97	2.2	72.39
18	45.13	2.53	94.39
19	34.03	1.94	94.29

ter aspiration of the cyst followed by injection with alpha interferon. Four patients who further complained of headaches became asymptomatic after further treatment with applications of alpha interferon. The 14 remaining patients underwent further treatment cycles due to persistence of the cyst or its return to the initial dimensions.

Table 3 displays the data on the patients regarding age, gender, previous treatment, catheter installation method, number of cycles, total dose administered, initial and final measurements, reduction rates, follow-up time and side effects.

DISCUSSION

The main objective of treatment for craniopharyngioma has always been the removal of the greatest possible amount of the tumor in order to minimize the risk of recurrence. This resection should be accompanied by no or minimal functional loss, which is all the more important in children, as the inherent risks of surgical treatment are more substantial in this population.

Most craniopharyngiomas that develop in childhood have characteristics that distinguish them from craniopharyngiomas diagnosed in adulthood, which makes their management more difficult. Indeed, childhood craniopharyngiomas are larger and more difficult to remove completely[7]. In children, cysts are present in 90% of all craniopharyngiomas. The adamantinomatous variant is prevalent, whereas the papillary or mixed type is rare.

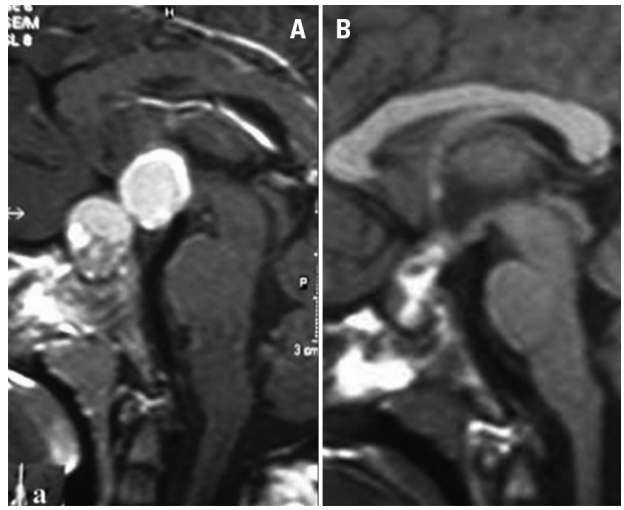

Fig 2. [A-B] Case 3: Bilobate craniopharyngioma and 3-year follow-up after intratumoral chemotherapy.

Table 3. Distribution of 19 patients regarding, age, gender, previous treatment, surgery, number of alpha interferon cycles, total dose (unit), initial and final volume (unit), reduction, follow-up and side effects.

Case	Age	Sex	Previous trmt	Surgery	Cycles	Total dose	Inicial size	Final size	Reduction	Follow-up	Side effects
1	18 y	F	yes	craniotomy	3	108,000,000	23.29	2.98	87.2%	21 m	headache
2	7y 11m	M	yes	craniotomy	2	72,000,000	54.08	4.69	91.32%	20 m	headache/fever
3	1y 10 m	M	no	craniotomy	4	144,000,000	35.04	0.81	97.68%	22 m	headache/fever
4	12y 8m	M	no	craniotomy	3	108,000,000	37.44	2.63	92.97%	45 m	depression/chronic fatigue syndrome
5	13y 5 m	M	no	craniotomy	2	72,000,000	12.87	1.71	86.71%	26 m	headache/fever
6	10y	M	yes	craniotomy	3	108,000,000	7.02	2.08	70.37%	17 m	headache
7	7y	F	yes	craniotomy	4	144,000,000	39	15.6	60%	20 m	headache/ eyelid erythema
8	6 y	M	no	craniotomy	2	72,000,000	3.36	0.14	95.83%	20 m	fever
9	10y 6m	M	no	craniotomy	2	72,000,000	9.79	0.94	90.39%	2y 4m	headache/fever
10	12y 2m	M	no	craniotomy	1	36,000,000	34.94	1.06	96.96%	2y 3m	fever/ eyelid erythema
11	11y	F	no	craniotomy	4	144,000,000	40.32	4.65	88.46%	20 m	headache
12	12y 9 m	M	no	craniotomy	1	36,000,000	52.32	3.57	93.17%	22 m	headache
13	19y 2m	M	no	neuroendoscopy	1	36,000,000	25.74	4.8	81.35%	23 m	headache/fever/ eyelid erythema
14	12y 4m	M	no	craniotomy	1	36,000,000	23.29	3.37	85.53%	17 m	NDN
15	19y	M	no	endoscopia	1	36,000,000	16.38	1.06	93.52%	17 m	headache
16	3y 7m	M	no	puncture	4	144,000,000	134.53	2.18	98.37%	24 m	headache/fever/ eyelid erythema
17	15y 4m	M	yes	craniotomy	1	36,000,000	7.97	2.2	72.39%	21 m	headache
18	7y 9m	M	no	neuroendoscopia	2	36,000,000	45.13	2.53	94.39%	22 m	
19	18y	M	no	craniotomy	2	36,000,000	34.03	1.94	94.29%	20 m	headache

Even after complete surgical removal, the incidence of recurrence is also high among children[3,7,8]. The retrochiasmatic variant, which is associated to significant impairment of the hypothalamus, accounts for approximately 50% of cases, whereas the purely intrasellar type is rare. Thirty percent of patients exhibit associated obstructive hydrocephalia. The reason for this complex behavior in childhood has not yet been fully clarified, but the early clinical manifestation of a tumor known to be of a congenital nature is believed to be related to more aggressive biological behavior[3,7].

According to reports from pediatric series and studies on mixed populations of patients, the lower rate of complete resections in children in comparison to adults demonstrates that technical difficulties are truly greater in the child population. Moreover, the postoperative period is particularly complex, especially with regard to the hydroelectrolytic balance and sudden fluctuations in natremic levels, which are difficult to control. Craniopharyngioma resection may cause hormonal deficiencies and vision impairment related to the location of the tumor. In the follow up of these children, there are reports of morbid obesity and alterations in complex cortex functions, such as memory and behavior, as well as learning disabilities[9-11]. The combination of these conditions severely compromises the quality of life of these children. Patients with craniopharyngioma have considerably lower quality of life indexes in comparison to healthy children and their social relations and emotional development are affected in a catastrophic manner, as craniopharyngiomas are mainly diagnosed in children at school ages[12,13].

All these considerations justify the enormous interest in the proposal of novel treatment modalities for craniopharyngiomas in children. The use of bleomycin was an effort to encounter a novel strategy for improving the results of craniopharyngioma treatment[14]. Bleomycin is particularly effective in the treatment of squamous cell carcinoma. It is believed that squamous cell carcinoma and craniopharyngioma have the same embryological origin and, thus, the use of bleomycin in the treatment of craniopharyngiomas has also achieved good results. However, bleomycin is a highly neurotoxic drug and severe complications may arise following its leakage through the walls of the cyst, which can even lead to death[15]. Such risk associated to a control of approximately 41% of cases submitted to this treatment[16] has led to the gradual disuse of bleomycin, which is currently only indicated for exceptional cases and recurrences.

In this context, alpha interferon emerges as a quite promising therapy, as it does not have the neurotoxic effects found with bleomycin. The antitumoral activity of interferons is due to their anti-proliferation, cytotoxic and maturational effects, with the simultaneous modulation in patient immune response. Interferons are glycoproteins pertaining to the cytokine family and are related to cell growth factor beta and tumor necrosis factor, which are responsible for the control of cell differentiation and proliferation[17].

The efficacy of alpha interferon is well established regarding its activity against squamous cell carcinoma of the skin, in which it induces apoptosis[18]. Ikić et al.[19,20] were the first to use the intratumoral application in the treatment of squamous cell carcinoma, demonstrating a reduction and even disappearance of this tumor.

Jakacki et al.[21] were the first to use systemic alpha interferon in the treatment of recurring craniopharyngiomas and those that did not respond to conventional treatment. Based on the fact that craniopharyngiomas and squamous cell carcinomas have the same embryological origin and that squamous epithelium is characteristically found in both the cyst wall and solid component of the craniopharyngioma, a phase II study was carried out on a group of 15 patients between 4.2 and 19.8 years of age. Three patients who demonstrated a complete response (defined as the complete radiological disappearance of the tumor) had had predominantly cystic tumors. In the study, all patients experienced episodes of fever in the first weeks of treatment, accompanied by muscle cramps and myalgia. Seven patients developed important signs and symptoms of alpha interferon toxicity, which led to either the interruption of treatment or a reduction in the doses administered.

In 2002, Chamberlain[22] was the first to use an intraventricular application of alpha interferon for the treatment of neoplastic meningitis. The manifestations of neurotoxicity (described mainly as chronic fatigue syndrome) were easily treated and did not impede the continuation of treatment.

In the present study, 3,000,000 units of alpha interferon were administered to the interior of the cyst three times a week for four weeks, empirically. Moreover, the administration pathway has not been previously used and was justified by the possibility of administering a greater concentration of the drug in the interior of the cyst and, consequently, a greater and more prolonged exposed of the tumor cells to the action of the agent. The authors found no reports in the literature on the intratumoral administration of alpha interferon in brain tumors or intracystic administration in cases of craniopharyngiomas. This type of therapy was based on the authors' previous experience with the treatment of craniopharyngiomas using bleomycin[14,23].

The need for the administration of new cycles was established based on the clinical or radiological response of the tumor. Moreover, the Kruskall-Wallis test revealed no differences in the reduction of tumor volume in relation to total number of cycles administered.

All patients (100%) experienced an important reduction in tumor volume at the end of treatment. The mean initial volume was 33.50 cm^3 and mean final volume was 3.10 cm^3. The reduction in tumor volume was greater than 90% in eleven patients (57.89%), between 81 and 87% in five patients (26.31%) and only three patients (15.78%) had less important reductions in tumor volume, but these reductions were still 60, 70 and 72%. The variability in response suggests the individual susceptibility of each patient, whether related to the characteristics of each tumor or the immune system of each patient.

The fluid aspirated at different times in the chemotherapy cycle was analyzed to determine whether the volume of the tumors was actually controlled by the successive mechanical aspirations. In 2007, the authors[24] published the results of the analyses of tumor necrosis factor-related apoptosis in the different samples of intracystic fluid, demonstrating the alpha interferon indeed plays an important role in the induction of apoptosis through a non-mitochondrial pathway in craniopharyngioma cells, leading to cell death[24]. The degree of apoptosis mediated by the FAS-ligand is only one of the factors of apoptosis[24]. Other non-mitochondrial apoptosis pathways mediated by caspases are currently under study.

The literature states that fatigue is the most frequent side effect[22] and main limiting factor to treatment with alpha interferon. In the present study, however, headache was the most frequent symptom. No patient needed to interrupt the treatment and, although no hormonal deficit was added to the preexisting deficits, one patient developed diabetes insipidus after the installation of the intratumoral catheter.

The most important aspect in the adoption of this treatment is the change in strategies established for the treatment of cystic craniopharyngiomas in childhood. Patients with craniopharyngioma live with a chronic disease and are subject to periods of intensified symptoms or deterioration that could be treated with the application of intratumoral alpha interferon. Provided these children experience improved vision, recover normal hormone levels, grow normally, attend school, exhibit adequate cognitive performance and neuropsychomotor development with minimal or no impairment to quality of life in this important age group, a further application of the chemotherapy cycle is believed to be less aggressive than an additional surgical intervention or sessions of radiotherapy. However, as this is a new treatment modality, a greater follow up time is needed to assess the effectiveness of alpha interferon in the long-term control of craniopharyngioma.

Health care professionals in charge of the treatment of childhood craniopharyngioma should be familiar with all forms of treatment and should demonstrate considerable skill in conducting different treatment modalities in order to provide better quality of life to patients, selecting the most adequate individualized option in each specific case.

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