Intracystic treatments for craniopharyngioma

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Craniopharyngioma is a benign tumor histopathologically and in theory should be curable by radical resection. In practice, this tumor behaves like a chronic disease, with many issues related to the effect of the tumor itself and the various treatments on the adjacent structures, such as the pituitary stalk and gland, hypothalamus, visual apparatus, and suprasellar arteries. A multimodality approach to the management of these tumors may produce the optimal outcome, balancing disease control and quality of life. In this paper, the role of intracystic therapies is reviewed, with the major focus on intracystic bleomycin and interferon-α. (DOI: 10.3171/2010.1.FOCUS09315)

Key Words • craniopharyngioma • intracystic therapy • radiotherapy • bleomycin • interferon

**C**raniopharyngiomas are histologically benign tumors, extrinsic to the brain parenchyma. As such, the ideal treatment of craniopharyngiomas should be complete resection, which might be expected to result in a cure with preservation of patient function. Unfortunately, the tumor may present with irreversible loss of visual, hormonal, and/or hypothalamic functions, and all treatments have the potential to produce additional deficits. As a result, children with these tumors suffer from a chronic disease process. The goal of treatment is tumor control and improved length of survival, while maintaining quality of life. To achieve this goal, one needs to consider the multiple potential interventions that exist for management of craniopharyngiomas, including surgery, radiotherapy, and intracystic treatments. One then needs to choose the intervention or interventions that are most appropriate for the individual, based on the anatomy of the tumor, patient age, and clinical picture (medical history and examination findings).

The location of the tumor, with variable involvement of the pituitary stalk and gland, the optic nerves and chiasm, the carotid and anterior cerebral arteries, and the hypothalamus, makes radical resection difficult, risky, and often technically impossible. In most recent patient series, gross-total resection of craniopharyngiomas was achieved in only 50 to 80% of attempted radical resections,⁷,⁴⁰,⁴⁵,⁵¹ although there are rare reports of much higher success rates.¹² Furthermore, even when total resection of the tumor has been achieved, and confirmed by CT scans and MR imaging, recurrences occur in 10 to 30%,¹¹,¹³,⁴⁷ with more recurrences revealed the longer one follows these patients.

Radical resection usually results in loss of anterior pituitary hormonal function and diabetes insipidus, and may also be complicated by visual deterioration. Most devastating is the complication of hypothalamic injury, with development of life-long morbid obesity and neurocognitive changes.³⁶,⁴⁰ Using the standard intracranial approaches for resection, tumors that, on MR imaging, appear to be anterior to the hypothalamus or are simply pushing the floor of the third ventricle upwards are those most amenable to complete resection without loss of hypothalamic function.⁵⁷ It may be that, in this group of patients, attempted radical resection should be the first line of treatment. For the tumors that appear to invade the hypothalamus on MR imaging scans, especially if children with these tumors already have clinical evidence of hypothalamic dysfunction, the risks of radical resection are higher and thus there is a role for considering alternative approaches to treatment.

The most commonly used alternative treatments for craniopharyngiomas have been a biopsy procedure, cyst drainage, or planned partial resection, followed by EBRT. Based on studies of patients treated mainly in the 1960s and 1970s, 10- and 20-year progression-free survival rates of approximately 80% have been achieved using conventional fractionated radiotherapy.²⁴,³⁸,³⁹,⁴⁵ This approach
has resulted in less early morbidity, but there have been significant problems that occurred later, including visual loss, hormonal deficiencies, decreased memory and intellect, moyamoya disease, strokes, and rarely, a secondary neoplasm. More modern techniques of radiotherapy, including proton beam therapy, conformal radiotherapy, intensity modulated radiotherapy, and stereotactic radiotherapy and radiosurgery might be expected to reduce the long-term complications while preserving the positive results of radiotherapy.13,14,31,32 For any type of radiotherapy, the potential for complications is higher the younger the child, so that any management protocol that delays the use of radiotherapy may be beneficial.31

One of the typical characteristics of craniopharyngiomas is the presence of a cyst within the tumor. Such cysts occur in more than 90% of tumors and often the cyst comprises the major component of the tumor.2 This characteristic has led to another line of therapy, specifically instillation of antineoplastic agents into the tumor, including beta-emitting radionuclides, bleomycin, and IFNα into the cyst. In this review, the focus will be on the use of bleomycin and IFNα.

**Intracystic Beta-Emitting Radionuclides**

The first intracystic therapy comprised the use of radioactive beta-emitting radionuclides, such as phosphorus32, yttrium96, rhenium186, and aurum198, and this treatment is reviewed here only briefly. The beta-emitting radionuclides are instilled after stereotactic puncture of the cyst and the appropriate dose is calculated on the basis of the size of the cyst. The goals of intracavitary radiotherapy are reduction of the cyst and long-term control of the tumor, in many respects similar to the goals of EBRT. Regardless of the beta-emitting radionuclide used, intracavitary radiotherapy reduces the size of the cyst in 50 to 100% of cases, according to different case series.6,23 Patient survival at 10 years after this treatment is also good, ranging from 45 to 80%.9 However, in the longest followed series of patients reported, survival continued to decline over time, falling to < 20% after 20 years and 0% by 30 years.23 New endocrinopathy is very unusual after intracystic radiotherapy, but visual loss and radionecrosis of the hypothalamic or pontomesencephalic regions have been noted in approximately 5% of patients, and vascular involvement with moyamoya disease or subarachnoid hemorrhage more rarely.2,23 One of the negatives of intracavitary radiotherapy is the small number of facilities with access to the radioisotopes and the complexity of the process for instillation of such materials into the cyst.

**Intracystic Bleomycin**

More recently, bleomycin has been used for intracystic treatment of craniopharyngiomas, both initially and at the time of recurrence. At one center, bleomycin has been proposed as a treatment that can provide durable control of the tumor.24 However, in general, bleomycin has been used for temporary tumor control with the expectation that other therapies, such as resection or radiotherapy, will be required for longer term tumor control. In that respect, the goals of treatment are different from those of intracavitary radiotherapy.

Takahashi et al.43 first reported the use of intracavitary bleomycin after partial excision of craniopharyngiomas. Subsequently, there have been a number of single-center case series5,16,16,22,25,27,33,33 and case reports1,3,9,17,26,41,42 published on the use of intracavitary bleomycin for craniopharyngioma, both as de novo treatment and as treatment for recurrences. In addition, the experience of intratumoral bleomycin use across multiple centers in Canada has been reviewed.19 In a detailed review of all reports of intracystic bleomycin for brain tumors up to 2007, Linnert et al.28 identified 189 cases, of which 130 were craniopharyngiomas. In the craniopharyngioma group, 1 series of 9 patients16 was part of a later report,19 and 1 report is misquoted and should include 3 rather than 8 patients,25 so that, in fact, there were no more than 116 patients treated, some of whom underwent concomitant radiotherapy. The response to bleomycin therapy was not reported. We have reviewed the published data and have identified 100 patients included in series of 10 or more patients who were treated with intracystic bleomycin for craniopharyngioma. The outcomes of these patients are summarized in Table 1.

Bleomycin is usually injected into the craniopharyngioma cyst via a subgaleal Ommaya reservoir attached to a catheter, with its tip located in the craniopharyngioma cyst. Many approaches have been used to insert the catheter into the cyst. These approaches include an open subfrontal or pterional approach with direct visualization of the tumor, a transcortical approach, and a transcortical transventricular approach, often supplemented by intraoperative ultrasonography, endoscopy, and/or stereotaxy. One of the concerns with the transventricular route is that there may be toxic effects from spillage of the cyst contents into the ventricular system.2 However, such spillage has not caused any ill effects in our experience.16 Real-time ultrasonography or endoscopy is helpful in directing the catheter into the cyst, especially when the cyst wall is tough. It is important to avoid leakage of the bleomycin

<table>
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<th>Authors &amp; Year</th>
<th>No. of Patients</th>
<th>% Patients w/ Cyst Shrinkage</th>
<th>Mean Follow-Up (yrs)</th>
<th>% Progression-Free at Last Follow-Up</th>
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<td>59</td>
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<td>20</td>
<td>62</td>
<td>NA</td>
<td>85</td>
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* NA = not available.
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outside the cyst into the subarachnoid space, because this may be toxic. Thus, it is important to position all the holes at the tip of the catheter within the cyst.

The standard ventricular catheters typically have holes starting 3 mm behind the tip, and continuing as far back as 1.8 cm from the tip, so that the cyst needs to be at least 2 cm in diameter to allow all the holes to be within the cyst. We have used a modified catheter containing holes that go back only 8 mm from the tip to make the margin of safety greater. Furthermore, to minimize leakage around the catheter, we try to insert the catheter using a push technique with a stylet in place or a minimal incision, if one is using an open approach to visualize the cyst directly.16 Intraoperative ultrasonography also allows the surgeon to place the catheter tip deeply in the cyst and to know exactly where the tip is located. Postoperatively, prior to instilling bleomycin, contrast material is injected into the Ommaya reservoir, the head of the child is shaken vigorously, and a CT scan is performed to confirm that there is no leakage of contrast material outside the cyst. If there is leakage, a CT scan with intracystic contrast enhancement may be repeated in 1 or 2 weeks, by which time the leakage is usually no longer present. If there is no leakage, the first dose of bleomycin is instilled. Some of the fluid in the cyst is aspirated from the Ommaya reservoir and is replaced with a smaller volume of bleomycin, followed by a 1-ml flush of normal saline. The intent is to keep the volume of the cyst stable during the injection, with no attempt made to collapse the cyst by excessive aspiration, because that could cause the holes in the catheter to be outside the wall of the cyst.

The appropriate dose and frequency of intracystic bleomycin use have not been defined in a scientific manner. The usual dose per instillation has been between 2 and 5 mg, with the larger dose used for larger cysts. Generally, bleomycin has been used 3 times per week, but some centers have used it daily. The treatment is continued for up to 5 weeks, or until the fluid in the cyst becomes fairly clear. Lactate dehydrogenase levels in the cyst fluid gradually decrease with treatment and have been used by some investigators to determine when to discontinue treatment, but we have not found that useful. When the tumor did not respond to the first course of bleomycin, additional courses of the drug have been used.19 In the Canadian experience,19 the median total dose administered during the first course was 36 mg (range 8–75 mg) and the median total dose of bleomycin was 55 mg (range 15–115 mg). The median dose/kg/week was 0.43 (range 0.17–1 dose/kg/week). The median dose of a single injection, in terms of concentration within the cyst, was 0.09 mg/ml/dose (range 0.01–2 mg/ml/dose).

Intracystic bleomycin is effective in inducing at least more than 25% shrinkage of the craniopharyngioma cyst in up to 90% of patients, with a more than 90% reduction in cyst size in approximately 25% of patients.19 At a mean follow-up of 2 to 7 years (the range of means for the studies), 43 to 70% of patients required no treatment in addition to bleomycin,5,16,19,31,42 but there is no information about the durability of the bleomycin effect at 10 years or longer. In the Canadian experience,19 which is similar to the other reported series, 94% responded to intracystic bleomycin, but the duration of response was < 1 year in 47%. Sustained benefit was noted in 53% for a median of 14 months (range 15–107 months). However, in our experience, progression of the tumor inevitably occurs with longer follow-up, and we have noted tumor progression in 2 patients as long as 8 and 10 years after excellent responses to bleomycin. Importantly, in the Canadian series, radiation therapy was delayed by a median of 43 months (range 2–112 months), which is particularly important in the youngest children, in whom there is the most concern about adverse effects from radiotherapy.

The acute morbidity of intracystic bleomycin includes transient mild fever, nausea, vomiting, or headache, which occur in as many as 70% of patients, typically 24 hours after each instillation, and are self-limiting.19 More importantly, there are delayed complications, which are rare, but serious. In a review of the complications of intracystic bleomycin in 189 patients with brain tumors, Linnert et al.28 identified 5 patients (3%) with severe adverse effects and 6 patients (3%) with moderate adverse effects. Reported delayed complications include sensorineural hearing loss,5,14 peritumoral edema,19 visual loss,33,35 hypothalamic dysfunction resulting in transient hyperosmolarity, personality changes, poor memory,17,35 cerebral ischemia,5 hemiparesis,22,35 progressive panhypopituitarism,19 precocious puberty,19 and death possibly related to radiation therapy in 2 patients as long as 8 and 10 years after excellent response.18 There have been a number of reported cases of moyamoya disease after intracystic bleomycin treatment for craniopharyngioma in patients who have also received radiotherapy, and it may be that radiotherapy sensitizes the vessels to bleomycin or vice versa.19,29

The effects of intratumoral bleomycin on future resection, if required, are not clear. Some neurosurgeons have stated anecdotally that there appeared to be more adhesions around the tumor and others have indicated that they believed that tumor resection was easier after bleomycin use. In cases in which the pathology was examined after bleomycin use, there were no unusual features to the tumor or its vasculature following recurrence and subsequent resection.19

In summary, intratumoral bleomycin has a limited role in the management of predominantly cystic craniopharyngiomas, in which an attempt at total resection is believed to be inappropriate or in which delay of other treatment such as EBRT is desirable. This therapy may result in control of the cyst for a variable period of time and may allow delay of radiotherapy or radical resection, which may be beneficial, especially in very young children. In the occasional case of what is believed to be an unresectable tumor, reduction of the cyst may change the assessment of the resectability of the tumor and allow an attempt at complete resection. The use of intracystic bleomycin does have some potentially serious complications and it may be possible that a similar effect can be achieved more safely with the use of IFNα, as described below.

Intracystic IFNα

As an alternative to bleomycin, intracystic IFNα has been used for patients with craniopharyngiomas.9,20 The
loss of appetite, and behavioral changes.20 Cavalheiro has noted that a cyst appeared white on the T1 sequence of MR imaging started after 30 days if the cyst did not decrease or if the cyst became solid. At minimum, the tumor was less adherent than a typical cystic tumor and delay more definitive treatment aimed at longer term control. Unlike bleomycin, IFNα has similar advantages to intracystic bleomycin, but does not appear to have any significant major toxicity, even if it spills into the subarachnoid space. As such, use of IFNα would appear preferable to bleomycin as an intracystic treatment for craniopharyngiomas, but further reported series would allow a stronger recommendation in this regard as the experience with this treatment remains small and long-term follow-up is not well documented at this stage.

Conclusions

Craniopharyngioma is a benign tumor pathologically and in theory should be curable by radical resection. In reality, this tumor behaves like a chronic disease, with many issues related to the impact of the tumor itself and the various treatments on the adjacent structures, such as the pituitary gland and stalk, hypothalamus, visual apparatus, and suprasellar arteries. A multimodality approach to the management of these tumors may provide the optimal outcome, balancing disease (tumor) control and quality of life, which is the goal of managing any chronic disease. As part of the multimodality armamentarium, intracystic therapies with bleomycin and most recently IFNα have a role, particularly in the predominantly cystic craniopharyngiomas. Currently, of these 2 intracystic modalities, IFNα appears to have fewer side effects, but experience is limited and further studies are awaited.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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