Hydroxyurea Treatment of Meningiomas: A Pilot Study

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ABSTRACT

Objectives: To present a pilot study of hydroxyurea chemotherapy in the management of surgically difficult meningiomas. **Design:** Prospective case series. **Setting:** Tertiary referral center. **Participants:** Six patients were enrolled: five had symptomatic recurrent or residual WHO Grade I meningiomas and one had an unoperated anterior clinoidal meningioma. **Main outcome measures:** MRI volumetry before and after treatment, hematological state, progression to surgery. **Results:** Hydroxyurea was administered for 1 year, starting at a dose of 15 mg/kg/day. No tumors reduced in size on treatment and one continued to grow rapidly. Three remained stable. Full volumetry was unavailable on two patients. One patient was withdrawn from the study because of myelosuppression and underwent further surgery. Three experienced significant drug-related side effects. Two patients underwent further surgery. **Conclusions:** From this small pilot study we conclude that although hydroxyurea may be associated with disease stabilization in some patients, it did not reduce tumor mass and it caused significant side effects in some of our subjects.

KEYWORDS: Hydroxyurea, chemotherapy, meningioma

Meningiomas are common (with an incidence of at least 4 to 6 per 100,000 per year)¹ and the majority are histologically benign.² The need for a

new therapeutic modality is clear: surgery is still the treatment of choice^{3,4} but may prove inadequate in tumors which are hard to remove completely

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because of their location. In such cases, recurrence is often a problem.^{5,6} In some patients surgery may be impossible or associated with an unacceptable morbidity. Radiotherapy has been widely advocated but rarely reduces tumor size¹ and may be complicated by long-term side effects.^{7,8} Other largely unsuccessful therapeutic options have included hormone therapy,⁹ immunotherapy,¹⁰ and chemotherapy.¹¹

In 1997, two papers emerged from Erlangen, Germany^{12,13}. The first of these demonstrated hydroxyurea-induced apoptosis in meningiothelomatous tissue in vitro and in vivo. Hydroxyurea is an oral antimetabolite whose main use is in the treatment of chronic myeloid leukemia. The mechanism of action is not clearly established but it appears to inhibit ribonucleotide reductase and causes apoptosis in phase S of the cell cycle.¹² Frequently reported side effects include myelosuppression, nausea, and skin reactions.

The second paper claimed marked success in reducing meningioma tumor bulk in four patients following the administration of hydroxyurea. Subsequent trials attempting to reproduce these promising results have been disappointing, although more modest responses to the drug have been reported in all cases.^{5,14,15} Here, we present our experience with hydroxyurea in the treatment of patients with meningioma.

MATERIALS AND METHODS

The case series was conducted with full ethics committee approval and informed consent. The

entry criteria were age (16 to 65), nature of tumor (surgically inaccessible or recurrent WHO Grade I meningioma), and radiological progression. In all cases, more conventional treatment options had been exhausted.

Efficacy and safety assessments: MRI volumetry was recorded at baseline. Safety outcome measures were twofold: hematological (via weekly FBC monitoring) and clinical (via observation and reporting of common side effects).

Treatment regimen: Hydroxyurea was started under hematological supervision at 15 mg/kg/day orally and increased gradually to the maximum tolerated dose based on neutrophil count and side-effects profile. After 12 months, hydroxyurea was stopped and each patient was reassessed clinically and with MRI volumetry. Patients were then reassessed 12 months later.

RESULTS

Six patients were enrolled in the study. Patients were all female with a mean age of 46. Five had symptomatic recurrent or residual WHO Grade I meningiomas and one had an unoperated, radiologically diagnosed left anterior clinoidal meningioma.

MRI Volumes

For a summary of these results, see Table 1. Formal MRI volumetry was unavailable for three patients (Patients 1, 4, 6). No tumors reduced in size

Table 1 MRI Volumes in cm³

Patient Number	Gender	Age	Pathology	Time on Treatment	Baseline MRI	MRI 2	MRI 3
1	Female	24	Grade I meningioma	2 months	—	—	—
2	Female	43	Grade I meningioma	13 months	40.5	42.0	42.5
3	Female	32	Grade I meningioma	13 months	40.5	42.0	41.5
4	Female	63	Grade I meningioma	4 months	—	35.0	35.0
5	Female	61	Clinoidal meningioma	12 months	92.5	104.0	113.0
6	Female	53	Grade I meningioma	11 months	51.5	—	—

on treatment. One continued to grow rapidly (Patient 5). In two patients, tumor size remained stable (Patients 2, 3, 4).

Safety

One patient was withdrawn from the study after 2 months because of myelosuppression and nausea and vomiting (Patient 1). An additional three (Patients 2, 3, 6) experienced significant drug-related side effects, not requiring drug cessation, in the form of cold sores and bruising, gingivitis, and a UTI, respectively.

Progression to Surgery

Two patients required further surgery, the patient who was removed from the study because of marrow suppression (Patient 1) and the patient whose tumor increased markedly in size (Patient 5).

DISCUSSION

In selecting patients for our study, exclusion criteria were those with another malignancy or marrow suppression and women of child-bearing age not on a reliable contraceptive. In those admitted to the case series, hydroxyurea appeared to stabilize disease progression in three of our patients.

There have been no true successors to Schrell's 1997 paper¹³ in its reporting of dramatic

tumor reduction of meningioma following the administration of hydroxyurea. Equally, however, subsequent studies have been unable categorically to rule out the possibility of any clinical benefit from the drug when used in this context. In 2000, Newton and coworkers¹⁴ entered 17 patients with residual or irresectable meningioma into a hydroxyurea trial. Although no actual tumor mass reduction was observed, of the 16 eligible for evaluation, 14 achieved stable disease with very little overall toxicity (although none of these tumors were known to be enlarging at the time of treatment). In 2002, these findings were echoed in the study by Rosenthal and associates,¹⁵ with a high degree of drug tolerance and 11 patients achieving disease stabilization. In 2002, Mason and his colleagues⁵ reported a minor, partial, temporary reduction in tumor mass in 1 of their 20 patients on hydroxyurea but, perhaps more significantly, they achieved stable disease in a further 12 patients on the drug. In 2003, Paus and colleagues¹⁶ published a case report outlining yet another case of clinical stabilization of an optic nerve sheath meningioma following treatment with hydroxyurea. These data are summarized in Table 2.

The fact that Schrell's dramatic results with hydroxyurea in the treatment of meningioma have not been reproduced in subsequent trials is not an argument for the failure of the drug in the neurosurgical context. Since surgery and radiotherapy have been proven to be problematic in many cases of meningioma, any added benefit from a chemotherapeutic agent should be considered seriously. The clinical course of these tumors is so varied that evaluating new forms of treatment and

Table 2 Summary of Previous Findings in Treatment of Meningioma with Hydroxyurea

Study	Patients Evaluated/ Entered	Tumor Regression	Tumor Progression	Stabilization of Disease
Schrell et al ¹³	4/4	4	0	0
Newton et al ¹⁴	16/17	0	2	14
Rosenthal et al ¹⁵	13/15	0	2	11
Mason et al ⁵	20/20	1	7	12
Paus et al ¹⁶	1/1	0	0	1

comparing these with the gold standard presents a real challenge.

CONCLUSION

Our small study of six patients treated with hydroxyurea suggests the possibility of a clinical role for this drug in stabilizing progressive disease in some patients. Where further surgery is not an option and radiotherapy has already been performed, this may be of modest benefit.

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