Stabilization of disease progression by hydroxyurea in patients with recurrent or unresectable meningioma

WARREN P. MASON, M.D., FRED GENTILI, M.D., DAVID R. MACDONALD, M.D., SUBRAMANIAN HARIHARAN, M.D., CHARLENE R. CRUZ, R.N., AND LAUREN E. ABREY, M.D.

Department of Medicine, Princess Margaret Hospital, and the University of Toronto; Division of Neurosurgery, Department of Surgery, Toronto Western Hospital and the University of Toronto; Departments of Medical Oncology and Neurology, London Regional Cancer Centre and the University of Western Ontario, New Jersey Neuroscience Institute, Edison, New Jersey; and Department of Neurology, Memorial Sloan-Kettering Cancer Center, New York, New York

Object. The management of certain meningiomas of the skull base and those involving the dural venous sinuses remains a challenge. In recent reports it has been suggested that hydroxyurea chemotherapy can cause regression of unresectable and recurrent meningiomas. The authors report their experience in using hydroxyurea for the treatment of patients with recurrent or unresectable meningiomas.

Methods. Hydroxyurea was administered at a dosage of approximately 20 mg/kg/day to 11 women and nine men (median age 59 years, range 31–75 years) with recurrent or unresectable intracranial meningiomas (12 basal, two parasagittal, and six multiple). In 16 patients the meningiomas were benign, in three they had atypical features, and in one the meningioma was malignant. All patients had measurable residual disease. Four patients with benign meningiomas had previously received radiotherapy (two were treated with conventional fractionated radiotherapy and two with stereotactic radiosurgery), three with atypical meningiomas received conventional fractionated radiotherapy, and the one with a malignant meningioma received conventional radiotherapy with additional stereotactic radiosurgery. Tumor enlargement was documented in all patients on neuroimages obtained before initiation of hydroxyurea therapy.

All patients were evaluable for response to therapy. In 12 patients with benign meningiomas, the disease had stabilized on neuroimages obtained posttreatment (median duration of treatment 122 weeks, range 8–151 weeks), and two of these showed clinical improvement. One patient with a benign meningioma experienced a minor partial response that was noted after 39 weeks of treatment and was confirmed on neuroimaging and clinical evaluations. In three others with benign meningiomas, progression was confirmed on neuroimages obtained after 41, 55, and 66 weeks, respectively; the 1-year freedom from progression rate was 0.93 (standard error 0.07) in patients with benign meningiomas. In three patients with atypical meningiomas, the tumors had progressed on neuroimages obtained after 12, 19, and 45 weeks, respectively. In the patient with a malignant meningioma, progression was confirmed on neuroimages obtained after 24 weeks. Hydroxyurea has been reasonably well tolerated, although one patient discontinued therapy because of moderate myelosuppression.

Conclusions. Although tumor regression appears uncommon, these results indicate that hydroxyurea may arrest progression of unresectable or recurrent benign meningiomas.

KEY WORDS • meningioma • brain neoplasm • malignant tumor • hydroxyurea • chemotherapy

Abbreviations used in this paper: KPS = Karnofsky Performance Scale; MR = magnetic resonance; NCI = National Cancer Institute; SE = standard error.
sion-free survival rates of 83% in patients with subtotal-
ly resected benign meningiomas. Although radiosurgery is an emerging modality that spares the surrounding brain damaging effects of irradiation, this approach has also been associated with significant complications, including cranial nerve injury and peritumoral edema.

Additional treatment options for patients with recurrent meningiomas who are no longer candidates for surgery or radiotherapy have included hormone therapy, immunotherapy, or chemotherapy. Hydroxyurea is a chemotherapeutic agent that is useful in the management of chronic myelogenous leukemia. Hydroxyurea can be used for years with acceptable and reversible toxicity, and for this reason it may be an optimal drug for treatment of a slowly growing tumor with a low mitotic index, such as a meningioma, in which protracted exposure to a chemotherapeutic agent is desirable.

Recently, Schrell, et al. reported dramatic responses to chronic daily treatment with hydroxyurea in three patients with recurrent benign meningiomas and in one with a malignant meningioma. This unexpected and promising observation prompted us to evaluate the efficacy of hydroxyurea in patients with recurrent or unresectable and enlarging meningiomas.

Clinical Material and Methods

Patient Selection

Criteria for initiating hydroxyurea therapy included the following: 1) histologically confirmed diagnosis of meningioma as defined by the criteria of the World Health Organ-

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>KPS Score</th>
<th>Dx From Dx (mos)</th>
<th>Tumor Location</th>
<th>No. of Previous RT (mos)</th>
<th>Neurological Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>benign meningiomas</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>74</td>
<td>M</td>
<td>90</td>
<td>26 falcine</td>
<td>3</td>
<td>—</td>
<td>seizures</td>
</tr>
<tr>
<td>2</td>
<td>66</td>
<td>F</td>
<td>70</td>
<td>240 CS</td>
<td>2</td>
<td>—</td>
<td>HA, ophthalmoplegia, optic atrophy, hearing loss</td>
</tr>
<tr>
<td>3</td>
<td>62</td>
<td>F</td>
<td>80</td>
<td>253 petroclival</td>
<td>7</td>
<td>—</td>
<td>trigeminal neuropathy, facial paresis</td>
</tr>
<tr>
<td>4</td>
<td>45</td>
<td>F</td>
<td>60</td>
<td>68 multiple</td>
<td>1</td>
<td>—</td>
<td>multiple cranial neuropathies</td>
</tr>
<tr>
<td>5</td>
<td>56</td>
<td>F</td>
<td>90</td>
<td>108 petroclival</td>
<td>1</td>
<td>—</td>
<td>trigeminal neuropathy, hearing loss, facial paresis</td>
</tr>
<tr>
<td>6</td>
<td>57</td>
<td>F</td>
<td>90</td>
<td>38 CS</td>
<td>1</td>
<td>—</td>
<td>ophthalmoplegia, optic atrophy, trigeminal neuropathy</td>
</tr>
<tr>
<td>7</td>
<td>41</td>
<td>F</td>
<td>70</td>
<td>123 CS</td>
<td>3</td>
<td>—</td>
<td>ophthalmoplegia, optic atrophy</td>
</tr>
<tr>
<td>8</td>
<td>47</td>
<td>F</td>
<td>90</td>
<td>108 CS</td>
<td>3</td>
<td>—</td>
<td>ptosis, trigeminal neuropathy</td>
</tr>
<tr>
<td>9</td>
<td>60</td>
<td>F</td>
<td>80</td>
<td>96 CS</td>
<td>2</td>
<td>—</td>
<td>ophthalmoplegia, optic atrophy</td>
</tr>
<tr>
<td>10</td>
<td>51</td>
<td>M</td>
<td>60</td>
<td>24 petroclival</td>
<td>2</td>
<td>—</td>
<td>ophthalmoplegia, optic atrophy</td>
</tr>
<tr>
<td>11</td>
<td>63</td>
<td>F</td>
<td>90</td>
<td>144 multiple</td>
<td>1</td>
<td>SRS (108) ataxia</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>70</td>
<td>M</td>
<td>100</td>
<td>44 CS</td>
<td>2</td>
<td>RT (42) optic atrophy</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>31</td>
<td>M</td>
<td>90</td>
<td>88 CS</td>
<td>3</td>
<td>—</td>
<td>optic atrophy</td>
</tr>
<tr>
<td>14</td>
<td>63</td>
<td>F</td>
<td>80</td>
<td>11 multiple</td>
<td>1</td>
<td>RT (6) seizures</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>40</td>
<td>M</td>
<td>50</td>
<td>46 falcine</td>
<td>1</td>
<td>SRS (37) hemiparesis</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>75</td>
<td>M</td>
<td>70</td>
<td>37 multiple</td>
<td>4</td>
<td>—</td>
<td>HA, seizures, ophthalmoplegia, hearing loss, hemiparesis, ataxia</td>
</tr>
</tbody>
</table>

malignant or atypical meningiomas

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>KPS Score</th>
<th>Dx From Dx (mos)</th>
<th>Tumor Location</th>
<th>No. of Previous RT (mos)</th>
<th>Neurological Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>57</td>
<td>F</td>
<td>70</td>
<td>41 multiple (malignant)</td>
<td>3</td>
<td>RT &amp; SRS (17) seizures</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>67</td>
<td>M</td>
<td>70</td>
<td>38 multiple (atypical)</td>
<td>5</td>
<td>RT (20) seizures, aphasia, hemiparesis</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>53</td>
<td>M</td>
<td>80</td>
<td>103 sphenoid wing (atypical)</td>
<td>2</td>
<td>RT (24) impaired memory, trigeminal neuropathy, facial paresis</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>63</td>
<td>M</td>
<td>80</td>
<td>209 sphenoid wing (atypical)</td>
<td>6</td>
<td>RT (2) aphasia, facial paresis</td>
<td></td>
</tr>
</tbody>
</table>

* CS = cavernous sinus; Dx = diagnosis; HA = headaches; HU = hydroxyurea; RT = conventional radiotherapy; SRS = stereotactic radiosurgery; — = none.
ceived conventional irradiation, two underwent stereotactic radiosurgery, and one received both conventional radiotherapy and stereotactic radiosurgery. All patients had completed radiotherapy at least 2 months before starting hydroxyurea therapy (median 22 months, range 2–108). Twelve patients with benign meningiomas (75%) entered this study without having undergone previous radiotherapy, and all patients with malignant or atypical meningiomas had received radiotherapy before starting hydroxyurea therapy. No patient had received chemotherapy before starting treatment with hydroxyurea. Patients were enrolled in this study a median of 78 months after the initial diagnosis (range 11–253 months). All patients were symptomatic on entry to the study. All patients had evidence of tumor progression on neuroimages obtained before initiation of hydroxyurea therapy.

Treatment Protocol

Patients were treated between June 1997 and September 1999; all patients were screened for compliance and met eligibility criteria. A single dosage of hydroxyurea was administered daily (20–30 mg/kg/day; usually 1000 or 1500 mg daily). Treatment was continued until there was evidence of progression on neuroimaging or clinical follow-up review or for a maximum of 2 years. For patients who experienced significant drug toxicity (NCI: common toxicity criteria Grade 3 or higher), hydroxyurea was administered at a dosage of 80 mg/kg/day every 3rd day.

Observation and Evaluation

For the 1st year of treatment, patients underwent serial MR imaging of the brain (with and without gadolinium enhancement) every 3 months. Complete blood counts were obtained every 2 weeks, and liver and renal function was evaluated monthly. Neurological and physical examinations were performed monthly, and KPS scores were assigned. After 1 year of therapy, MR images were obtained every 6 months, and physical examinations were performed every 2 months.

We used MR images to assess neuroimaging response. The initial tumor cross-sectional area was determined by multiplying the longest length of the enhancing tumor by its perpendicular measures. A complete neuroimaging response was defined as total disappearance of all enhancing tumor for a minimum of 4 weeks. Patients were required to discontinue steroid drugs and to be neurologically stable or improved. A partial response was defined as at least a 50% reduction in tumor size in comparison with the baseline MR image. Patients had to be neurologically stable or improved on a stable or decreasing dose of dexamethasone. Progressive disease was defined as at least a 25% increase in enhancing tumor or the appearance of new lesions. Patients had to be neurologically stable or worse while taking a static or increasing dose of steroid drugs. Stable disease or neuroimaging encompassed all other situations.

Clinical response was defined as improved, stable, or worse, where improved implied objective clinical improvement on a static or decreasing dose of corticosteroid drugs, stable meant a stable neurological status on a static or decreasing dose of corticosteroid drugs, and worse meant a deterioration of neurological status on a static or increasing dose of corticosteroid drugs.

Side effects and toxicities were graded using the NCI common toxicity criteria (version 2.0).25 Therapy with hydroxyurea was discontinued if the following toxicities persisted after dose modification: absolute neutrophil counts less than 1000/mm³, platelet counts less than 50,000/mm³, intractable nausea or vomiting unresponsive to antiemetic drugs, recrudescence of radiation dermatitis, and renal or hepatic toxicity that was NCI Grade 3 or higher.

Statistical Analysis

The sample size used here was not based on considerations of statistical power, but rather on the number of patients available over the study period. The freedom from (further) progression curve was calculated from the initiation of treatment with hydroxyurea by using the method of Kaplan and Meier. Patients who were free of progression at the time of analysis were censored.

Results

By the end of the study, all patients had discontinued hydroxyurea chemotherapy and were evaluable for response assessment and toxicity; these results are presented in Table 2.

Clinical and Neuroimaging Response Rate

Sixteen patients had meningiomas that were benign on pathological examination. The progression-free rate for this cohort is presented in Fig. 1. The 1-year and 2-year freedom from progression rates are 0.93 (SE 0.07) and 0.77 (SE 0.12), respectively. A minor response on neuroimaging that did not meet formal criteria for a partial response was seen after 39 weeks of treatment in one patient who had a benign meningioma (Fig. 2). Clinical improvement in this patient’s aphasia and hemiparesis was also noted. Twelve patients with benign meningiomas had stable disease on neuroimaging for a median of 122 weeks (range 8–151 weeks). Two of these patients had clinical improvement: one experienced significant reduction in the frequency and severity of headaches and periorbital pain caused by tumor-associated palsy, and one had fewer headaches. One patient with a benign meningioma that stabilized after administration of hydroxyurea underwent subsequent surgical debulking of her tumor for attempted palliation of persistent symptoms and continued to receive hydroxyurea postoperatively without disease progression. Three patients with benign meningiomas had progressive disease at 41, 55, and 66 weeks, respectively.

Three patients had atypical meningiomas. In one disease, progression was confirmed on neuroimages obtained 45 weeks after a period of stabilization, and in the other two, the disease progressed after 12 and 19 weeks of treatment, respectively. In the patient with a malignant meningioma, disease progression was confirmed on neuroimaging at 24 weeks.

Side Effects

Treatment with hydroxyurea was well tolerated, and toxicity was largely myelosuppressive in the majority of patients, with anemia and neutropenia being the most commonly observed hematological abnormalities. No patient
Response to and toxicity of hydroxyurea therapy in 20 patients with recurrent or progressive meningiomas

<table>
<thead>
<tr>
<th>Duration</th>
<th>Tumor Response</th>
<th>Toxicity (NCI criteria)</th>
<th>Adjunctive Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case No.</td>
<td>(wks)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

benign meningiomas

1  41  SD→PD  —  —  surgery
2  97  SD (HA improved)  Grade 2 hematological (Hg)  —  —  surgery
3  55  SD→PD  —  —  —  —  RT
4  132  SD  Grade 2 hematological (Hg)  —  —  —  —  —
5  114  SD  Grade 2 hematological (Hg, WBC, Plt), Grade 2 hepatic  —  —  —  —
6  127  SD  —  —  —  —
7  142  SD  —  —  —  —
8  128  SD  Grade 2 hematological (Hg)  —  —  —  —
9  120  SD  —  —  —  —
10  151  SD  —  —  —  —
11  61  SD  —  —  surgery
12  8  SD  Grade 3 hematological (Hg, WBC)  —  —  —  —
13  52  SD  Grade 3 hematological (WBC)  —  —  —  —
14  39  mPR  Grade 3 hematological (WBC)  —  —  —  —
15  124  SD  —  —  —  —
16  66  SD→PD (HA improved)  —  —  RT

malignant or atypical meningiomas

17  4  PD  —  —  —  —
18  12  PD  Grade 2 hematological (Hg)  —  —  —  —
19  45  SD→PD  —  —  surgery
20  19  PD  —  —  —  —

* Hg = hemoglobin; mPR = minor partial response; PD = progressive disease; Plt = platelets; SD = stable disease; WBC = white blood cells.

experience NCI Grade 4 toxicity; NCI Grades 2 and 3 hematological toxicity was noted in eight patients. Five patients continued hydroxyurea therapy after dose reduction, two continued therapy without dose modification, and one discontinued therapy because of myelosuppression. Transfusions or growth factors were not required for patients who experienced hematological toxicity. No patient developed an infection or required antibiotic drugs because of treatment-related neutropenia. In one patient who was receiving hydroxyurea, a diagnosis of acute myelogenous leukemia was made. Nonhematological toxicity was noted in one patient who had NCI Grade 2 elevation of hepatic transaminases that required no intervention.

Discussion

A recent anecdotal report in which the authors used neuroimaging to document objective responses of benign meningiomas to hydroxyurea chemotherapy generated a great deal of interest and prompted this study in which patients with recurrent or progressive meningiomas were treated with hydroxyurea for a period of 2 to 5 years.33 Before beginning therapy, all patients had worsening symptoms, measurable residual tumor after the most recent resection, and documented neuroimaging evidence of tumor progression. A minority of our patients had received radiotherapy before starting hydroxyurea treatment. For these patients, however, the interval between completion of radiotherapy and the onset of symptomatic and neuroimaging-confirmed progression was considerable, thereby reducing the likelihood that the observed worsening was a delayed effect of radiotherapy and not genuine tumor progression. Treatment was continued for a maximum of 2 years because we believed that a tumor with a low mitotic index would require protracted exposure to cell cycle-specific cytotoxic therapy before a response might be noted.11

In contrast to the dramatic objective responses of four patients with meningiomas reported by Schrell, et al.,33 we observed only one minor partial neuroimaging-confirmed response in a patient with a benign meningioma. Hydroxyurea was effective, however, in halting the tumor growth in 12 patients (75%) with benign meningiomas in which progression was documented on neuroimaging. Although the duration of follow up has been brief, we are encouraged by the estimated 1- and 2-year freedom from progression rates of 0.93 (SE 0.07) and 0.77 (SE 0.12), respectively, for the 16 patients with benign enlarging meningiomas who received hydroxyurea therapy. Furthermore, improved symptoms were reported in the patient who had a minor partial response recorded on neuroimaging and in two additional patients with benign meningiomas who achieved neuroimaging-confirmed stability. In our series, the few patients with atypical and malignant meningiomas did not benefit from hydroxyurea therapy, and all of their lesions progressed on clinical and neuroimaging evaluations after a brief exposure to this agent.

Treatment was generally well tolerated, and most patients could remain on therapy without dose adjustment. As anticipated, toxicity was almost exclusively hematological and was reversible with dose reduction or discontinuation of treatment. Hydroxyurea is used conventionally for prolonged periods for the treatment of chronic myelogenous leukemia and the management of sickle cell disease. In situations in which patients are treated for years with this drug, delayed toxicities include hepatic injury and secondary hematological malignancies. In our series one patient did develop acute myelogenous leukemia while receiving hydroxyurea therapy. We believe that the development of this malignancy was unrelated to the treatment, because her leukemia did not demonstrate the typical cytogenetic de-
Stabilization of meningiomas treated with hydroxyurea

rangements observed in leukemias induced by cytotoxic agents. Furthermore, this patient continued to receive hydroxyurea as palliative chemotherapy for the leukemia.

Our results are similar to those of Newton, et al.,27 who treated 17 patients who had unresectable or residual meningiomas. In our study, 88% of patients responded to treatment with neuroimaging-confirmed stabilization of disease for a median duration of 80 weeks. No patient experienced neuroimaging-confirmed regression of tumor, and no clinical benefit from therapy was discerned. The spectrum and severity of drug-related toxicities observed by Newton, et al., was similar to those reported in the present study. In contrast to our study, in which all patients had enlarging tumors, 11 of 17 patients treated by Newton, et al., had no evidence of clinical or neuroimaging-confirmed progression at the initiation of therapy. Consequently, the rate of disease stabilization reported by those authors may be overestimated.

It is not clear how hydroxyurea halts the growth of meningiomas. It exerts its antiproliferative effect by the inhibition of ribonucleotide reductase, thereby preventing DNA synthesis, and leading ultimately to cell death during the S phase of the cell cycle.4,10,15,17 Recent work by Schrell, et al.,32 has demonstrated that hydroxyurea can induce cell apoptosis in cultured meningioma cells and meningioma transplants in nude mice. The mechanism by which hydroxyurea induces apoptosis has not been elucidated.

Meningiomas often progress after surgery and radiotherapy, and a number of medical therapies have been used in an effort to control their growth. Attempts to control the growth of recurrent meningiomas with chemotherapeutic agents such as cyclophosphamide, Adriamycin and vincristine, or immune-modulating agents such as interferon-α have had only modest success.3,12 Reports have been anecdotal, have included small numbers of patients, and have failed to provide convincing evidence of therapeutic efficacy. Moreover, toxicity associated with the use of these agents has been considerably greater than that observed in our study. Recently, hormone therapy with the antiprogestrone agent RU-486 has aroused interest, but results of a randomized placebo-controlled phase III study have not been sufficiently encouraging to stimulate further development of this treatment modality for meningiomas.8

Our series of patients is unique because the majority of those with benign meningiomas had not received radiotherapy for tumor progression. In cases in which radiotherapy was declined, the main factor that influenced this decision was the concern about delayed toxicity from cranial irradiation, including cranial nerve deficits and cognitive dysfunction.5,34 Accumulated evidence indicates, however, that radiotherapy does appear to arrest the growth of recurrent and residual benign meningiomas, and it is the conventional nonsurgical treatment for this disease. Nevertheless, benign meningiomas do eventually progress after maximal radiotherapy, and there is a need for new nonsurgical approaches to the management of this disease. As demonstrated in our series of patients, irradiation is usually incorporated early in the management of atypical and malignant meningiomas; evidence for its beneficial impact on the behavior of these aggressive neoplasms at this early stage is convincing.22,28

The few patients with malignant or atypical meningiomas who have been treated with hydroxyurea did not appear to derive significant benefit from treatment. Our study indicates, however, that hydroxyurea can arrest the growth of enlarging benign meningiomas. Benign meningiomas have a long natural history and can unpredictably enter prolonged periods of dormancy.29 For this reason, it is difficult to study the impact of therapeutic interventions on the course of this disease. In our experience, hydroxyurea is unlikely to cause regression of benign meningiomas. Nevertheless, standard response criteria for brain tumors as formulated by Macdonald, et al.,20 were developed for malignant neoplasms, in which regression is possible and represents a reliable measure of efficacy. Low-grade tumors such as meningiomas have a proliferation index of less that 1% and may not demonstrate neuroimaging-confirmed regression as a response to treatment.11 Consequently, conventional response criteria may not be the most suitable method for evaluating novel approaches to the management of these indolent neoplasms, in which stabilization of growth may represent a beneficial and clinically significant outcome.

In this study, a majority of benign meningiomas in which progression was documented on neuroimaging studies had stabilized on hydroxyurea therapy for approximately 2 years, at which point treatment was discontinued. Furthermore, in our series, 19% of patients with benign meningiomas who achieved disease stabilization with this therapy experienced clinical improvement. These observations are encouraging; it seems that hydroxyurea has a positive impact on the behavior of enlarging benign meningiomas, and the data provide preliminary support for its use in this group of patients, who often have limited therapeutic options. Hydroxyurea is an ideal candidate therapy for indolent tumors such as meningiomas because it is an orally administered agent that can be taken safely for a prolonged duration. Our results indicate that hydroxyurea may have an emerging if limited role in the management of disease in patients with benign meningiomas and that it is worthy of further study in this population. This drug appears to be particularly suitable for those who have unresectable benign meningiomas that have progressed after initial surgery or maximal radiotherapy or for those who wish to delay or avoid cranial irradiation or further surgery.
Acknowledgment

We thank Dr. Tony Panzarella for reviewing this manuscript and for providing statistical assistance.

References


Manuscript received August 23, 2001. Accepted in final form April 29, 2002. Address reprint requests to: Warren P. Mason, M.D., Princess Margaret Hospital, Suite 18-717, 610 University Avenue, Toronto, Ontario, M5G 2M9 Canada. email: warren.mason@uhn.on.ca.