

Hydroxyurea chemotherapy in the treatment of meningiomas

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✓Meningiomas are slow growing, extraaxial tumors that derive from the arachnoidal cap cells of the meninges. Resection remains the main modality of treatment and can be curative in some cases. External-beam radiotherapy and radiosurgery can benefit selected patients. The role of chemotherapy continues to be defined, but should be considered for patients with inoperable or frequently recurring meningiomas. Hydroxyurea, an inhibitor of ribonucleotide reductase, is one of the most active agents and is known to induce apoptosis in meningioma cells in vitro and in mouse xenografts. Results of preliminary clinical studies suggest that hydroxyurea has modest activity against recurrent and inoperable meningiomas, and can induce long term stabilization in some patients. However, the results are conflicting and a few clinical trials did not show positive results. Further clinical trials with larger patient cohorts and longer follow-up periods will be necessary to confirm the activity of hydroxyurea. (DOI: 10.3171/FOC-07/10/E11)

KEY WORDS • apoptosis • chemotherapy • hydroxyurea • meningioma • ribonucleotide reductase

Introduction and General Overview

Meningiomas are usually slow growing, benign tumors of extraaxial origin that arise from the arachnoidal cap cells associated with the arachnoid villi at the dural venous sinuses, cranial nerve foramina, cribiform plate, and medial middle fossa.^{4,6,9,36} Meningiomas are classified by their site of origin within the nervous system, which is most commonly the intracranial cavity. In adults 85 to 90% of tumors occur supratentorially, with 30 to 40% arising along the base of the anterior and middle fossae.⁵⁰ The most common sites are the parasagittal or falx region (25%), convexity (19%), sphenoid ridge (17%), and suprasellar area (10%). In children, meningiomas occur more commonly within the posterior fossa and ventricular system.

Meningiomas account for 18 to 20% of all intracranial tumors in most series.^{9,28,47,64} The frequency appears to be similar among studies conducted in North America, Europe, and Japan. However studies of African populations suggest an elevated frequency (mean 30.1%, range 24–38%).^{9,32} The incidence rates vary across different studies, from 0.08 to 13.72 cases per 100,000 people, with an overall incidence of 2.6 per 100,000.⁴⁶ Older data have sug-

gested that incidence rates may be higher among African-Americans than Caucasian Americans. However, more recent surveys show an equal incidence in the United States between the two groups.⁶³ Most studies support an increased incidence in females, with male/female ratios ranging from 1:1.4 to 1:2.8. However, the ratio may be more equal in African and African-American populations. The incidence of intracranial meningiomas increases with advancing age; the authors of older studies have suggested a peak in the seventh decade for men and the eighth decade for women.⁵⁰ More recent data from the Central Brain Tumor Registry of the United States⁶⁴ have shown that the incidence continues to increase beyond 85 years of age without reaching a peak.

For the majority of patients in whom a meningioma develops, its origin remains unclear.^{4,9,36,47,64} Potential etiologic factors that have been investigated include radiation exposure, cranial trauma, viruses, hormonal stimulation, and molecular genetic events. The most consistently documented factor appears to be prior cranial radiation exposure. Meningiomas have been shown to be induced by low- and high-dose irradiation.^{47,51,60,64} To meet the criteria for a radiation-induced tumor, the mass must arise within the irradiated field, develop after a period of latency following irradiation (20–30 years), and be histologically different from any preexisting neoplasm in the region.

The signs and symptoms in patients harboring meningiomas are quite variable and depend on the location of the tumor within the intracranial cavity.^{6,9,50} Symptoms refer-

Abbreviations used in this paper: CCA = calcium channel antagonist; MR = magnetic resonance; NCI = National Cancer Institute; RR = ribonucleotide reductase; WHO = World Health Organization.

able to chronic increased intracranial pressure (such as papilledema and sixth cranial nerve palsy) can occur, but only with the largest tumors. In general meningiomas are slow growing, so the onset and worsening of symptoms are gradual. Overall the most common symptoms are headache and hemiparesis, which occur in 36 and 30% of patients, respectively.⁵⁰ Other frequent symptoms include seizures, gait difficulty, visual abnormalities, confusion, memory deficits, and personality changes.

Once a meningioma has been discovered on computed tomography scans or MR images, its location must be correlated with the patient's symptoms to determine if the tumor is incidental or causally related. If the symptoms do not match the tumor location and the tumor appears benign based on imaging criteria, then a period of observation with serial MR images obtained every 6–12 months is appropriate.^{1,6,8,9,36} This strategy is reasonable because it is well known that approximately 35–60% of meningiomas will spontaneously stop growing and remain dormant for various lengths of time.^{25,43} Once tumor growth is demonstrated on neuroimaging, a more definitive intervention can be pursued. Resection is the mainstay of treatment for intracranial meningiomas;^{1,6,8,9,36} complete resection of the tumor, its associated dural margins, and any involved bone is the goal in all patients. However, this is not possible in many cases due to the tumor's location (the cavernous sinus or medial sphenoid wing, for example) or involvement with delicate neurovascular structures such as the carotid artery. In addition, it is usually difficult to completely resect atypical and malignant meningiomas due to extensive infiltration along the dura mater and invasion of the underlying cortex or major venous sinuses. External-beam radiotherapy should be considered for selected patients with meningiomas;^{1,6,8,9,36} this is a viable option for patients who cannot undergo or refuse surgery. Radiation therapy is not indicated after gross-total resection of histologically benign meningiomas but may be beneficial in subtotally resected tumors or those with atypical or malignant features.^{35,37} In addition, radiotherapy may be active against tumors at the time of recurrence or progression. Effective doses are in the range of 4500 to 6000 cGy for benign tumors, and 6000 to 6500 cGy for malignant tumors. These doses should be administered in 180- to 200-cGy daily fractions over 5 to 6 weeks.³⁵ Stereotactic radiosurgery is a newer radiation modality that has been applied to meningiomas in recent years.^{1,8,9,36} Radiosurgery can be performed using a linear accelerator or the Gamma Knife within a well-defined intracranial volume that contains the tumor, with minimal exposure of normal brain tissue. The median effective total dose reported by most authors is 15 Gy (range 13–20 Gy).

Chemotherapy of Meningiomas: Overview

The role of adjuvant chemotherapy in patients with meningiomas remains unclear and continues to evolve.^{1,6,8,9,26,36,40,62} Chemotherapy has been applied mainly to inoperable lesions, especially in the setting of tumor progression or recurrence after some form of radiotherapy. Numerous approaches have been taken, including the use of traditional cytotoxic drugs, molecular agents, immunomodulators, and hormone-manipulating drugs. Although none of these drugs have been particularly effective, a modest activity in subgroups of patients has been demonstrated with some of

them. Chamberlain⁵ reported on the only conventional chemotherapy regimen that showed modest activity, which consisted of intravenous cyclophosphamide (500 mg/m²/day for 3 days), adriamycin (15 mg/m²/day for 3 days), and vincristine (1.4 mg/m² for 1 day). There were three patients with partial response to treatment and 11 with stable disease. The median time to tumor progression was 4.6 years, with a median survival of 5.3 years. Modest success has also been reported with interferon α -2B treatment (4 mU/m²/day, 5 days/week) in a small study of patients with unresectable and malignant meningiomas.²³ Of the six patients treated, one had a minor response to treatment and four had stable disease, with a mean time to progression of 8.3 months. Treatment with antiestrogenic agents, including a Southwest Oncology Group¹⁴ study using tamoxifen (40 mg/m² twice daily), has been generally ineffective.^{2,19,45,54} Initial results with the antiprogestone agent RU-486 (200 mg/day) were suggestive of activity. Five patients showed a minor response to treatment, and several others had stable disease and/or clinical improvement.^{16,27} However the phase III placebo-controlled trial of RU-486 was unable to demonstrate any significant evidence of activity.¹⁵ Molecular approaches to chemotherapy, using drugs such as imatinib and erlotinib that inhibit the growth factor receptors involved in the oncogenesis of meningiomas are also under study.⁶²

Hydroxyurea Chemotherapy

Basic Pharmacology, Clinical Applications, and Mechanism of Action

Hydroxyurea is a hydroxylated analog of urea with the molecular formula CH₄N₂O₂ and molecular weight 76.05 g/mol (Fig. 1).^{10,17,39} It was originally synthesized in Germany in 1869 by Dresler and Stein,¹¹ but was not applied to animals until 1928, when it was observed by Rosenthal and colleagues⁵² to induce leukopenia, anemia, macrocytosis, and death. In the late 1950s, hydroxyurea underwent further preclinical testing by Stearns et al.⁵⁸ and was noted to have significant activity in vitro against L1210 leukemia cells and various solid tumors.¹⁰ During the 1960s the drug was entered in oncological clinical trials and demonstrated significant efficacy against myeloproliferative disorders, as well as more modest activity against systemic solid tumors.^{10,17,39} Currently the principal therapeutic indication for using hydroxyurea is treatment of myeloproliferative disorders, chronic myelogenous leukemia and polycythemia rubra vera in particular. Other more recent clinical indications include sickle-cell anemia, HIV infection, thrombocytopenia, and psoriasis.^{17,30,39} In cancer patients, hydroxyurea has been extensively studied as a radiation sensitizer, since it is able to synchronize cells in a radiation-sensitive phase of the cell cycle and can also inhibit the repair of radiation-induced DNA damage.¹⁰ Radiosensitization has been evaluated in high-grade gliomas, non-small cell lung cancer, head and neck cancer, and cervical carcinoma. The most convincing evidence for added benefit has been seen in patients with advanced cervical cancer, with an increase in progression-free survival in the Stage III and IVA disease cohort.⁵⁹ Another application of hydroxyurea is the modulation of drug resistance in tumor cells.¹⁷ At clinically achievable concentrations, hydroxy-

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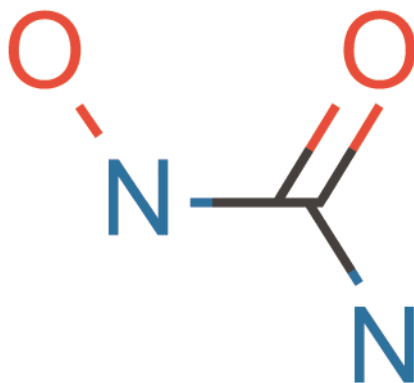


FIG. 1. Diagram of the molecular structure of hydroxyurea.

urea has been shown to accelerate the loss of extrachromosomally amplified genes with a subsequent increase in drug sensitivity.⁷

Hydroxyurea can exist in three tautomeric forms: a keto form and two imino forms.²⁴ The drug primarily adopts the keto form, which is significantly more stable than the imino forms (> 10 kcal/mol). Hydroxyurea contains three ionizable protons and behaves as a weak acid with a pKa of 10.6. In vivo hydroxyurea is converted to a free radical nitric oxide species along with other metabolic byproducts, while 30 to 50% of the drug remains unchanged.^{17,22,24} The drug and its active metabolites are transported by passive diffusion into cells, where they have their primary site of cytotoxic action—inhibition of the RR enzyme system.^{10,17} Ribonucleotide reductase is a tightly regulated enzyme responsible for the conversion of ribonucleotide diphosphates to the deoxyribonucleotide form, which is subsequently utilized in either de novo DNA synthesis or DNA repair processes.⁶¹ Hydroxyurea inhibits the activity of RR in vitro and in vivo, and the extent of inhibition of DNA synthesis correlates closely with the size of the decreased deoxyribonucleotide pools.⁶⁵ In humans and other mammals, RR consists of two subunits, referred to as M1 and M2.⁶¹ Subunit M1 contains the binding site for the substrates, as well as for allosteric effector sites; it is responsible for the complex regulation of the enzyme by cellular nucleotide pools. The M2 subunit is the catalytically active portion of the enzyme. Overall, RR is synthesized in low concentrations and its synthesis is the rate-limiting step in de novo synthesis of DNA.

Hydroxyurea inhibits RR activity by interacting with the tyrosyl free radical at the active site of the M2 subunit.^{10,17,24,39,65} Hydroxyurea selectively kills cells in S phase and, among S-phase cells, those that are synthesizing DNA at the highest rates will be most sensitive.⁶⁵ Treatment with hydroxyurea does not prevent cells from entering S phase. Cells appear to enter S phase at a normal rate, but accumulate or become blocked while in S phase, as a result of DNA synthesis inhibition. The cytotoxic effects of hydroxyurea correlate with the dose or concentration achieved, as well as with the duration of drug exposure.

In addition to specifically inhibiting RR, hydroxyurea also has a more global inhibitory effect on the replisome complex of tumor cells, which consists of DNA polymerases, thymidine kinase, dihydrofolate reductase, nucleoside-5'-phosphate kinase, thymidylate synthase, and RR.⁴⁹

This inhibitory effect only occurs in S phase and in intact cells and is probably due to a direct allosteric, structural interaction from a remote site within the complex.⁴⁶

Clinical Pharmacology of Hydroxyurea

Although hydroxyurea has been used clinically for over 40 years to treat oncology patients, its pharmacology and metabolism continue to remain somewhat incompletely understood in humans.^{10,12,17} The drug is usually administered orally and is well absorbed at clinical doses (20–30 mg/kg), crossing the intestinal wall by passive diffusion. Less than 1.0% can be recovered in the feces. In cancer patients, oral bioavailability to the systemic circulation is very good, ranging from 80 to 100% in various studies.¹⁷ Hydroxyurea has a volume of distribution that is approximately equal to the total body water content. Protein binding has not been thoroughly studied, but the drug appears to be 75 to 80% bound to serum proteins. At the tissue level, hydroxyurea enters cells via passive diffusion, including the brain and cerebrospinal fluid.^{3,17} Tissue concentrations of the drug equilibrate rapidly with levels in the serum. Therefore, blood concentrations can be used as an accurate reflection of the concentrations in tumor tissue. After attainment of peak plasma concentrations, hydroxyurea levels dissipate very rapidly, with an elimination half-life of 3.5 to 4.5 hours.¹⁰ Pharmacokinetic analysis suggests a one-compartment model and first-order renal excretion.¹⁷ The renal clearance at standard doses is roughly 90 ml/minute in the average patient. Due to the importance of renal clearance of hydroxyurea, it seems appropriate to modify doses for patients with abnormal renal function until individual tolerance can be evaluated. The metabolism of hydroxyurea occurs via renal and nonrenal mechanisms (presumably the liver).^{10,17} Between 30 and 50% of a given dose of the drug can be recovered as urea, with the majority of this biotransformation occurring in the liver and kidneys.

Preclinical Studies of Hydroxyurea

The first published reports of preclinical testing of hydroxyurea against meningiomas were made by Schrell and colleagues^{55,57} in the mid-to-late 1990s. Freshly resected meningioma tissue samples from 20 different patients were placed into primary early-passage cell cultures and then tested with the application of varying doses of hydroxyurea (10^{-5} – 10^{-3} M). A significant decrease in cell proliferation was noted at doses of 10^{-4} M ($p < 0.05$), and at 5×10^{-4} and 5×10^{-3} M ($p < 0.001$), including some tumors with a complete block of growth and others with a reduction in cell number. On DNA flow cytometric analysis, doses of 5×10^{-4} and 5×10^{-3} resulted in an increase in the percentage of cells in S phase (range 12–39%; $p < 0.001$) and G₂M phase, suggesting an S-phase block. Further analysis revealed tumor cells with fragmented nuclei, consistent with an apoptotic mechanism of cell death. When cultured tumor cells were transplanted intraperitoneally into nude mice and treated with hydroxyurea (0.5 mg/g body weight for 15 days), numerous apoptotic cells were noted.

Using a different approach, Ragel et al.⁴⁸ studied the effect of adding a CCA (diltiazem or verapamil) to hydroxyurea during treatment of meningioma cell cultures and xenografts. The results of prior studies had demonstrated

that CCAs can block *in vitro* and *in vivo* meningioma growth at clinically relevant doses.^{20,21} In the current report, meningioma surgical specimens were placed into primary cell cultures and also transplanted into mouse xenografts. All cell cultures were treated with hydroxyurea, RU-486, verapami, diltiazem, various drug combinations, or 0.1% ethanol vehicle control. Dose-dependent growth inhibition was noted in all meningioma cell lines (six benign and one malignant) after single-agent treatment with either hydroxyurea, RU-486, diltiazem, or verapamil. When verapamil or diltiazem in doses of 100 $\mu\text{mol/L}$ were added to hydroxyurea (0–50 $\mu\text{mol/L}$), the growth inhibitory effect against the malignant cell line was enhanced by approximately 40 to 50% over the use of hydroxyurea alone ($p < 0.05$, analysis of variance test). Growth inhibition was nominally increased with higher doses of hydroxyurea. Similar enhancement of growth inhibition was noted when either diltiazem or verapamil was added to RU-486. Treatment of benign cell lines also showed an enhanced growth inhibitory effect that ranged from 20 to 30% over hydroxyurea alone. *In vivo* testing with mouse flank xenografts using the same treatment paradigm demonstrated diminished growth rates of the benign and malignant tumors in comparison to controls. Growth inhibition was most marked when the combination of hydroxyurea and diltiazem was used (75–78% over controls).

Clinical Studies of Hydroxyurea

Due to the promising results noted in the preclinical studies, Schrell and colleagues^{55,57} felt that hydroxyurea was a potent inhibitor of meningioma cell growth and had significant potential as a therapeutic modality for patients with unresectable and rapidly growing meningiomas. They were the first to describe the use of hydroxyurea in patients with inoperable meningiomas, in a small pilot study reported in 1997 (Table 1).^{56,57} The study was open to any patient with a recurrent and unresectable meningioma. Four patients were enrolled (two men and two women), each with a tumor that had grown into or originated from the cavernous sinus. All patients included in the study had undergone previous attempts at resection (range 1–6 operations), and three had undergone external-beam radiotherapy. The cohort had a mean age of 48 years and a mean Karnofsky Performance Scale score of 70%. Three patients had WHO Grade I tumors and one patient had a malignant WHO Grade III tumor. Each patient was treated with hydroxyurea (20 mg/kg/day; equivalent to 1000, 1500, or 2000 mg/day) and was then monitored every 3 months. Significant enlargement was not noted in any of the tumors during the course of treatment. Two of the patients with Grade I meningiomas had 60 to 75% shrinkage over a 6- to 10-month follow-up period, as documented on serial MR images. In addition, one patient with tumor-related trigeminal neuralgia and abducens nerve paresis noted significant improvement in neuralgic pain and extraocular muscle function after 5 months of treatment with hydroxyurea. In a third patient with a low-grade tumor there was a 15% reduction in tumor size with resolution of trigeminal neuralgia pain after 5 months of treatment. The fourth patient, who harbored a malignant meningioma, was treated with hydroxyurea after a sixth palliative resection and did not have any shrinkage of tumor. However, the mass remained stable during 24 months of hydroxyurea therapy.

In a similar study, Mason and coworkers^{33,34} evaluated the activity of hydroxyurea over a 2-year treatment period (20–30 mg/kg/day) in a group of patients with recurrent or unresectable meningiomas (Table 1). The treatment cohort consisted of 20 patients (9 men and 11 women) with a median age of 59 years and a median Karnofsky Performance Scale score of 80%. All patients in the study had undergone at least one attempt at resection (range 1–7 previous operations), and eight of the patients had received some form of radiotherapy. Sixteen patients had WHO Grade I tumors, three had Grade II atypical tumors, and one had a Grade III malignant tumor. Tumor enlargement was documented in all patients before chemotherapy. In the subgroup of patients with low-grade meningiomas one patient had a minor response to treatment, growth remained stable in 12 (median treatment duration 122 weeks), and in three disease progression was demonstrated after a variable period of stabilization (after 41, 55, and 66 weeks of treatment). The 1- and 2-year freedom from progression rates were 93 and 77%, respectively, for patients with benign tumors. In several patients in this group, clinical improvement of symptoms was noted during treatment. In the subgroup with atypical meningiomas, tumor growth was stable in one patient for 45 weeks before progressing, while in the other two progression was noted after only 12 and 19 weeks. The one patient with the malignant meningioma had progressive disease after 24 weeks of therapy.

Based on the preliminary positive results from Schrell, Newton and associates^{41,42} reported on the use of hydroxyurea (20 mg/kg/day) in several papers with overlapping cohorts. The expanded cohort consisted of 21 patients (four men, 17 women), with a median age of 59 years (range 33–74 years).⁴¹ In 17 of the patients, at least one resection had been attempted (range 1–7 prior operations). Nine patients had had prior external-beam irradiation; none of the patients had had any prior chemotherapy. All of the tumors were WHO Grade I, except for one patient with an atypical meningioma (WHO Grade II). Eighteen of 20 evaluable patients (90%) had stable disease after treatment with hydroxyurea, with a median time to disease progression of 176 weeks (range 20–328 weeks). Five of the patients with stable disease eventually experienced disease progression after 20, 56, 36, 216, and 56 weeks of treatment. Two patients had rapid disease progression after only 10 weeks of therapy. In contrast to the Schrell and Mason studies cited above, no partial or minor response was noted on neuroimaging follow-up. In addition, none of the patients had neurological or symptomatic improvement while receiving hydroxyurea chemotherapy. Five patients were taken off hydroxyurea and placed on a chemotherapy hiatus; they remained stable at 328, 284, 286, 268, and 268 weeks of follow-up. Another patient was placed on hiatus after 216 weeks of treatment, but soon afterwards disease progression was noted. Overall, eight of 20 evaluable patients remained stable on MR imaging for longer than 4 years.

In a similar study, Rosenthal and colleagues⁵³ treated 15 consecutive patients (two men, 13 women) harboring recurrent or high-risk meningiomas with hydroxyurea (20 mg/kg/day) (Table 1). All of the patients had undergone surgery, but only one had received radiotherapy; none had received any form of chemotherapy. The median age was 39 years (range 24–79 years); 10 of the tumors were WHO Grade I, and five were WHO Grade II. None of the 13

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TABLE 1
Summary of clinical studies of hydroxyurea and meningiomas*

| Authors & Year | No. of Patients | Male/Female Ratio | No. w/ HU Pre-RT (%) | Response (No. of Patients) | No. w/ Stable Disease | Median TTP |
|------------------------|-----------------|-------------------|----------------------|----------------------------|-----------------------|------------|
| Schrell et al., 1997 | 4 | 2:2 | 1 (25) | partial (2) | 1 | — |
| Mason et al., 2002† | 20 | 9:11 | 12 (60) | minor (1) | 12 | — |
| Rosenthal et al., 2002 | 15 | 2:13 | 14 (93) | none | 11 | 44 wks |
| Fuentes et al., 2004 | 36 | — | — | minor (2) | 13 | — |
| Loven et al., 2004 | 12 | 5:7 | 6 (50) | minor (1) | 0 | 56 wks |
| Newton et al., 2004 | 21 | 4:17 | 12 (57) | none | 18 | 176 wks |
| Hahn et al., 2005† | 21 | 7:14 | NR‡ | minor (2) | 11 | — |
| Weston et al., 2006 | 6 | 0:6 | — | none | 3 | — |

* Abbreviations: HU = hydroxyurea; NR = not related; RT = radiation therapy; TTP = time to progression; — = not available.

† Studies with a 77% 2-year progression-free survival rate.

‡ This is a concurrent study of patients simultaneously treated with hydroxyurea and radiotherapy. Therefore, data regarding hydroxyurea treatment prior to radiotherapy are irrelevant.

evaluable patients achieved complete or partial response to treatment, 11 patients (85%) had stable disease for a median of 11 months (range 3–24 months), and two had progressive disease. Of the 11 patients with stabilization of disease, eight had documented tumor growth prior to the initiation of treatment with hydroxyurea.

In a more recent report, a patient was described with painless, right-sided visual loss who was noted to have a meningioma of the optic nerve.⁴⁴ Hydroxyurea was started (20 mg/kg/day) as the initial form of therapy, before irradiation or resection. After 7 months of treatment, the patient reported subjective improvement in vision. In addition, there was also improvement in formal visual field testing and normalization of visual evoked potentials after 10 months. The tumor remained stable on MR imaging and the patient was clinically improved during 18 months of follow-up evaluation.

Building on Schrell's earlier work, he and his colleagues¹⁸ have recently reported the results of a pilot study using the combination of hydroxyurea and concurrent conformal radiation therapy (Table 1). The cohort consisted of 21 patients (seven men and 14 women) with a median age of 60 years (range 34–76 years). The tumors were WHO Grade I in 13 cases, WHO Grade II in two cases, and WHO Grade III in two cases; four patients did not undergo surgery for histological confirmation and grade due to advanced age (median 71.5 years). Radiotherapy was delivered using 3D conformal planning, with a minimum dose of 50.4 Gy (median 55.80 Gy) for the low-grade tumors and a somewhat higher dose for the Grade II and III tumors. Hydroxyurea was taken daily at a dose of 1500 mg over a 12-week period. Of the 13 patients with Grade I tumors, 10 (77%) had SD for a median of 20 months (range 12–40 months). In two of these patients a minor response was eventually demonstrated on follow-up neuroimaging, clinical improvement was also noted. Three of the patients with low-grade tumors (23%) had progressive disease after treatment. In the atypical and malignant tumor cohorts, three of the four patients had stable disease for 4 to 34 months, with a median progression-free survival period of 13 months. Two of the four elderly patients whose disease was diagnosed by imaging remained stable after treatment for 10 and 19 months; the other two died of progressive disease soon after the completion of radiotherapy. The 1- and

2-year progression-free survival rates for the entire cohort were 84 and 77%, respectively.

In contrast to the studies outlined above, three other reports are less suggestive of the effectiveness of hydroxyurea against meningiomas (Table 1).^{13,31,63} Loven and colleagues³¹ describe 12 patients (5 men, 7 women) with unresectable, slow-growing tumors who received hydroxyurea at the usual dosing regimen over a 24-month observation period. All patients had undergone at least one resection (range 1–5 operations), and six of the patients had also received radiotherapy. Ten patients were evaluable: 7 were WHO Grade I and three were WHO Grade II. One patient had a minor response to treatment that lasted for the 24-month period of treatment, as well as clinical stabilization, while nine patients had progressive disease with a median time to progression of 13 months (range 4–24 months). The two remaining patients were withdrawn from the study due to severe hematological toxicity. In the study by Fuentes and coworkers,¹³ 43 patients with unresectable meningiomas were treated with hydroxyurea (20 mg/kg/day); 36 of these patients had had documentation of progression on MR imaging and/or clinical criteria at the beginning of chemotherapy. Twenty-eight patients had histological verification of disease; the tumors were WHO Grade I in 18 patients and Grade II in 10. Of the 36 evaluable patients, there were two (5.5%) with tumor shrinkage noted on MR imaging, 13 (36%) with disease stabilization, and 21 (58%) with tumor progression. In a pilot study, Weston and associates⁶³ enrolled six female patients with a mean age of 46 years (range 24–63 years). In five patients, tumor histological characteristics were verified as WHO Grade I. Hydroxyurea therapy was started at 15 mg/kg/day and administered for 1 year; dose escalation was allowable based on hematological status. In three patients the disease remained stable during the treatment period, while in one rapid progression was noted. The other patient was withdrawn from treatment due to myelosuppression.

Toxicity of Hydroxyurea

Regardless of the patient's diagnosis and schedule of drug administration, the dose-limiting toxicity of hydroxyurea is myelosuppression;^{10,39} an effect that is due to inhibition of DNA synthesis in the bone marrow. Megaloblastic changes can be detected in granulocyte and erythroid pre-

cursors within 48 hours of the initial dose. For patients with nonhematological malignancies and benign conditions, such as HIV infection and sickle-cell anemia, the peripheral white-blood cell count will begin to fall within 2 to 5 days of treatment initiation.^{10,29} Doses of 40 to 80 mg/kg/day induces leukopenia in the majority of patients within 14 days. Symptoms of gastrointestinal toxicity can include nausea, emesis, anorexia, and either diarrhea or constipation. However in most patients these symptoms are mild to moderate and only rarely require discontinuation of treatment. Patients who take hydroxyurea for long periods (months to years) may experience dermatological changes, including erythema of the face and hands, hyperpigmentation, maculopapular rash, and dry skin with atrophy.¹⁰ Changes may also be noted in the nail beds, such as atrophy or the formation of multiple pigmented nail bands. Severe skin reactions are rare and include an ulcerative dermatitis that resembles lichen planus. Headache, drowsiness, confusion, and dizziness have occasionally been reported but their significance remains uncertain. Rarely, transient abnormalities of renal function can occur, including elevation of serum urea nitrogen and creatinine, proteinuria, and an active urine sediment. Like other antimetabolites, hydroxyurea should be considered a potent teratogenic agent and should not be used in women of childbearing age unless proper contraceptive measures are in place.

In patients with meningiomas treated with hydroxyurea, the most commonly reported toxicity was also hematological.⁴⁰ In the reports by Schrell,^{56,57} these effects were mild. If the white-blood cell count fell below 3000/ μ l, the dose was reduced for several days, with subsequent improvement. Nonhematological side effects included mild fatigue, bleeding of the gums, and constipation. The cohort reported by Mason and associates³⁴ had similar myelosuppressive toxicity, with anemia and neutropenia being most common. There were no patients with NCI³⁸ Grade 4 hematologic toxicity, and NCI Grades 2 and 3 toxicity were noted in eight patients. Five of these patients continued hydroxyurea treatment after a dose reduction, two continued without a change in dose, and one had to discontinue treatment. However, transfusions of growth factors were not required for any patient. In addition, there were no infections associated with the episodes of neutropenia. Nonhematological toxicity was uncommon. Hematological toxicity was also the most common side effect in the reports by Newton et al.^{41,42} Grade 1/2 toxicity included leukopenia in nine patients, thrombocytopenia in seven patients, and anemia in five patients. Grade 3/4 toxicity was uncommon and included leukopenia in four patients and anemia in two patients. Growth factor injections were not required for any patients with NCI Grade 3/4 leukopenia, and no infectious complications were noted. Minor dosage reductions of 250 to 500 mg/day were necessary in 11 patients (52%) with hematological toxicity. The mean time-lag from initiation of treatment until dose reduction was 22.5 weeks. In each case, the dose reduction resulted in hematological stabilization and continued treatment. Nonhematological toxicity was uncommon and included mild fatigue (five patients; 23.8%) and mild elevation of uric acid levels (three patients; 14.2%) late in the course of treatment. The cohort described by Rosenthal et al.⁵³ had infrequent hematological toxicity and included two patients with Grade III neutropenia and thrombocytopenia and Grade I neutropenia

and anemia. Two of their patients developed significant skin rashes (NCI Grades II and III) that required cessation of hydroxyurea. In a chemoradiation study Hahn and coworkers¹⁸ suggested that hydroxyurea and concomitant conformal irradiation were well tolerated. Localized alopecia was noted in all cases, and two patients reported transient headaches, nausea, and vertigo. Grade I/II anemia and leukopenia were noted in four and eight patients, respectively. Five patients noted mild anorexia, weight loss, and nausea associated with chemotherapy. Severe NCI Grade III/IV hematological toxicity was noted in four patients (33%) in the study reported by Loven and associates.³¹ In two patients, toxicity improved after the dosage was reduced, while in the other two patients hydroxyurea therapy had to be discontinued. In the patients reported on by Fuentes et al.,¹³ hydroxyurea was relatively well-tolerated, with Grade I/II anemia and asthenia noted in 28 and 23.5% of patients, respectively. Treatment had to be discontinued in three patients due to chronic skin toxicity (one patient), and anemia and asthenia (two patients). The pilot study reported by Weston and colleagues⁶³ had a similar toxicity profile, with myelosuppression and some nonhematological side effects such as cold sores, bruising, and gingivitis.

Conclusions

Meningiomas are typically benign, slow-growing, extraaxial tumors, that are generally amenable to resection and radiotherapy. However, it is important that effective chemotherapy options be developed for these tumors since many patients cannot undergo surgery or, in some cases, may experience recurrence after resection and radiotherapy. Of the many chemotherapy options that have been evaluated in clinical studies, hydroxyurea remains one of the most promising agents; it has demonstrated modest clinical activity against inoperable and recurrent meningiomas and can often induce clinical and radiological stabilization. However, it should be emphasized that the data available are somewhat limited and contain a large proportion of patients that had received hydroxyurea before any form of radiotherapy (approximately 63%). Further studies of the use of hydroxyurea in the treatment of meningiomas with larger cohorts of patients, extended follow-up periods, and a more uniform exposure to radiation therapy, are necessary to fully characterize the effectiveness of this drug and determine how best to apply it. In addition, combination trials with other potentially active drugs such as imatinib and erlotinib will need to be implemented to fully explore the therapeutic potential of hydroxyurea.

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