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CLINICAL STUDY – PATIENT STUDY

Hydroxyurea for recurrent surgery and radiation refractory meningioma: a retrospective case series

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Abstract Hydroxyurea (HU), an orally administered chemotherapy, has become the de facto standard therapeutic agent in patients with surgically and radiation refractory meningiomas based on a limited literature. A retrospective case series of 60 patients with recurrent WHO grade 1 meningioma treated with HU following progression after surgery and radiotherapy was conducted with primary study objective progression free survival (PFS) at 6- and 12-months. Sixty patients (45 women; 15 men: median age 61.5 years, range 26–88) with recurrent meningioma were treated with HU (1000 mg/m^2/day orally divided twice per day; one cycle operationally defined as 4-weeks of daily HU). All patients had progressed radiographically after prior therapy with surgery (60/60) and radiotherapy (external beam radiotherapy 60/60; stereotactic radiotherapy 53/60). No patient received prior chemotherapy or targeted therapy before instituting HU. Patients received 1-12 cycles (median 2.0) of HU with modest toxicity (10% grade 3 + anemia or fatigue). There were no radiographic responses, 35% of patients had stable disease and 65% manifested progressive disease. Duration of stable disease ranged from 3 to 12 months (median 4.0 months). The overall PFS was 10% (median PFS 2.0 months). The majority of patients (80%) following progression on HU were subsequently treated on an investigational trial. In this retrospective case series, HU though generally well tolerated and convenient, appeared to have very limited activity which raises questions of what constitutes effective salvage therapy and indicates an unmet need for alternative treatments for recurrent meningiomas.

Keywords Hydroxyurea · Recurrent meningioma · Surgery and radiation refractory

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Introduction

Recurrent meningiomas are managed by re-resection when clinically indicated and surgically accessible, otherwise radiotherapy is most often employed [1–8]. At present there does not appear to be survival difference in treatment with stereotactic or conventional fractionated external beam radiotherapy and consequently either modality is used for recurrent disease [9, 10]. Not infrequently and as illustrated in the present retrospective series, sequential radiotherapy is employed for multiply recurrent meningioma. Less clear from the literature is how best to manage patients with surgery and radiotherapy refractory recurrent meningioma [11–24]. The 2010 Central Nervous System National Comprehensive Cancer Network (CNS NCCN) guidelines suggest three possible treatments (hydroxyurea, alpha-interferon or somatostatin analogues such as Sandostatin LAR) recognizing that there is very meager literature (medical level evidence category 3) regarding the medical oncology management of recurrent meningioma [12–19, 21, 22].

This retrospective case series of 60 patients represents experience in treating surgery and radiation refractory World Health Organization (WHO) grade 1 recurrent meningiomas with hydroxyurea (HU).

Patients and methods

A retrospective study of patients treated with WHO grade 1 meningioma with hydroxyurea was performed and evaluated patients treated between 1/2000 and 12/2009. Approval for the retrospective analysis was obtained from the university human investigation review committee.

Objectives and end points

The two primary objectives of this retrospective study included determination of efficacy and toxicity of HU in the treatment of adults with surgery and radiation refractory recurrent WHO grade 1 meningiomas. The primary end point of the retrospective analysis was progression free survival (6- and 12-month). Secondary end points included, time to progression and response.

Patient selection

Patients had histologically proven WHO grade 1 meningioma that was recurrent neuroradiographically. All patients had progressed following definitive radiotherapy (RT) and surgery and were not considered eligible for further RT or surgery. All patients were chemotherapy naive. At least 3-months had elapsed since prior radiotherapy. Patients had radiographically measurable disease wherein recurrent tumor was bi-dimensionally measurable (at least $1.0 \times 1.0\ cm^2$) by cranial contrast-enhanced magnetic resonance imaging (MR). Histological confirmation of tumor recurrence was not required. Patients had a Karnofsky performance status greater than or equal to 60 and a life expectancy greater than 3 months. Adequate hematologic, renal and hepatic functions were required. No serious concurrent medical illnesses or active infection could be present that would jeopardize the ability of the patient to receive HU therapy.

Drug schedule

Hydroxyurea (HU; Hydrea; Bristol-Myers-Squibb, NY) was administered orally for 28-consecutive days (1000 mg/m^2/day divided twice per day or rounded to the nearest dose level based on availability of HU capsule size) every 4-weeks (operationally defined as a cycle of therapy). HU was obtained commercially and billed to third party payers. No pharmaceutical sponsorship was provided in the conduct of this retrospective study. No premedication was required with oral HU. Concurrent medications included non-enzyme inducing anticonvulsants (20 patients), narcotics (15 patients), dexamethasone (15 patients), anti-constipation medication (14 patients) and anticoagulants (2 patients).

Treatment with HU was repeated every 28 days (4-weeks) provided that all toxicity from the previous cycle had resolved. If recovery had not occurred by day 28, the subsequent cycle of HU was delayed until recovery. All toxicities including hematologic due to HU therapy were rated retrospectively according to the NIH Common Toxicity Criteria (version 3.0).

Method of evaluation

All patients underwent cranial MR demonstrating progressive disease within 2 weeks of HU administration. Blood counts were obtained on day 1 of each HU cycle (or more often if clinically indicated), neurologic examination was performed every 4 weeks, and contrast-enhanced brain MR was performed after every two cycles of HU (i.e., every 8 weeks). Modified neuroradiographic response criteria as defined by Macdonald et al. were used [25]. All neuroradiography was reviewed by a neuroradiologist blinded to treatment and by the treating neuro-oncologist (MCC). Tumor measurements were determined by the neuro-oncologist (MCC). In patients with radiographic stable disease, partial response or complete response, 2 additional cycles of HU was administered and repeat MR was performed. Patients were continued on HU therapy until documentation of progressive disease at which time patients discontinued HU and were either monitored or offered alternative therapy. Alternative meningioma-directed therapy (or no therapy) was offered to patients that radiographically progressed.

Progression free survival (PFS) was defined as the time from the first day of treatment with HU until progression or death (PFS). Patients discontinued HU if there was progressive disease, development of unacceptable toxicity, patient refusal or noncompliance with treatment.

Results

Study population

Sixty patients (45 women; 15 men) ages 26–88 years (median 61.5), with recurrent WHO grade 1 meningioma (original and when applicable recurrent pathology reviewed and confirmed in all cases) were treated with HU (Table 1).

Patients presented at the time of tumor recurrence with the following signs and symptoms: worsening hemiparesis ($n = 22$), increased seizures ($n = 20$), headache ($n = 16$), gait disturbance ($n = 6$), and ophthalmoplegia ($n = 5$). Patient performance status using the Karnofsky scale

Table 1 Patient characteristics and treatment

#	Gender/age	Location	Initial therapy			Salvage therapy			HU therapy		
			Surgery	RT (Gy)	SRS	Surgery	RT (Gy)	SRS (Gy)	# cycles	Response	PFS
1	m/65	L frontal, L parietal, L cavernous sinus	STR	54	No	No	No	15	2	PD	2
2	m/84	L frontal, L temporal, falx	STR	54	No	No	No	14	2	PD	2
3	f/49	R cavernous sinus, R sphenoid wing	STR	54	No	STR x2	No	12	8	SD	8
4	f/68	L frontal	GTR	No	No	STR	54	No	2	PD	2
5	f/58	L parietal	STR	54	No	STR	No	15	8	SD	8
6	f/70	L sphenoid wing	STR	50.4	No	STR	No	15	6	SD	6
7	f/36	L temporal, L frontal	STR	54	No	STR X3	No	14	2	PD	2
8	f/55	L skull base/cerbellopontine angle	STR	55	No	No	No	14	8	SD	8
9	f/59	R sphenoid & cavernous sinus	Biopsy	54	No	No	No	12	2	PD	2
10	f/88	L frontal	GTR	No	No	STR	54	14	6	SD	6
11	f/54	R frontal	GTR	No	No	GTR	54	15	2	PD	2
12	m/66	L frontal, parietal	STR	55	No	STR	No	16	2	PD	2
13	f/57	R temporal	GTR	No	No	STR	54	15	2	PD	2
14	f/80	L cavernous sinus	Biopsy	54	No	No	No	12	2	PD	2
15	m/54	L frontal, R parietal	STR	54	No	STR x2	No	15	2	PD	2
16	f/87	L frontal	STR	54	No	No	No	12	2	PD	2
17	f/58	R frontal	STR	54	No	No	No	14	2	PD	2
18	m/69	L temporal	GTR	No	No	GTR	54	15	6	SD	6
19	f/66	R frontal	STR	54	No	No	No	14	8	SD	8
20	f/53	L parietal	Biopsy	54	No	No	No	18	2	PD	2
21	f/54	R frontal	STR	54	No	No	No	18	4	SD	4
22	f/66	L tentorium	STR	54	No	STR	No	14	4	SD	4
23	f/67	L cavernous sinus	Biopsy	54	No	No	No	18	4	SD	4
24	f/59	L frontal	GTR	No	No	STR	54	No	2	PD	2
25	f/61	L parietal	STR	54	No	No	No	18	2	PD	2
26	f/54	L parietal	Biopsy	54	No	No	No	14	1	PD	1
27	f/55	L frontal	STR	54	No	No	No	18	2	PD	2
28	f/66	L tentorium	STR	54	No	STR	No	14	2	PD	2
29	f/47	L frontal	GTR	No	No	No	54	15	1	PD	1
30	f/61	L frontal	STR	54	No	GTR	No	15	3	SD	3
31	m/61	R frontal-parietal	GTR	No	No	GTR x2	54	14	12	SD	12
32	m/62	L frontal, L fronto-parietal, R cavernous sinus	Biopsy	54	No	No	No	15	2	PD	2
33	m/83	L frontal, L temporal, falx, sphenoid sinus	STR	No	14	STR	54	No	2	PD	2
34	f/41	Cavernous sinus, L sphenoid wing	STR	54	No	No	No	14	4	SD	4
35	m/67	Bifrontal	GTR	No	No	STR	54	No	3	SD	3
36	f/55	L temporal-parietal	STR	54.5	No	No	No	13	2	PD	2
37	f/68	R sphenoid wing	STR	54	No	No	No	14	2	PD	2
38	f/26	R temporal, R frontal	GTR	No	No	STR	54	No	2	PD	2
39	f/45	R skull base/cerebellopontine angle	STR	No	No	No	54	14	2	PD	2
40	f/52	L sphenoid, cavernous sinus	Biopsy	54	No	No	No	15	1	PD	1
41	f/87	R frontal	STR	No	No	STR	54	14	3	SD	3
42	f/51	L frontal	GTR	54	No	STR	No	14	4	SD	4
43	m/61	R frontal, parietal	GTR	No	No	No	54	No	2	PD	2
44	f/51	R frontal	STR	54	No	No	No	15	2	PD	2
45	f/58	R occipital	GTR	No	No	STR	54	14	2	PD	2

Table 1 continued

#	Gender/age	Location	Initial therapy			Salvage therapy			HU therapy		
			Surgery	RT (Gy)	SRS	Surgery	RT (Gy)	SRS (Gy)	# cycles	Response	PFS
46	f/62	L cavernous sinus/sphenoid wing	Biopsy	54	No	No	No	15	4	SD	4
47	m/55	R temporal	GTR	No	No	STR	54	14	2	PD	2
48	f/69	L tentorial	STR	No	15	No	54	No	2	PD	2
49	f/70	L parietal	STR	54	No	No	No	15	4	SD	4
50	m/58	L frontal	GTR	No	No	GTR	54	No	6	SD	6
51	f/81	R tentorial	STR	No	14	STR	54	No	2	PD	2
52	f/75	R frontal	GTR	No	No	STR	54	14	2	PD	2
53	m/68	R parietal	GTR	No	No	No	54	14	2	PD	2
54	f/67	R cavernous sinus/sphenoid wing	Biopsy	54	No	No	No	15	2	PD	2
55	f/65	R frontal	STR	No	15	STR	54	No	4	SD	4
56	m/64	L frontal	GTR	No	No	No	54	14	2	PD	2
57	f/64	R frontal	GTR	No	No	STR	54	No	2	PD	2
58	f/65	L parietal falx	GTR	No	No	STR	54	15	2	PD	2
59	f/66	R frontal falx	STR	No	14	No	50	No	8	SD	8
60	m/60	Bifrontal	STR	54	No	No	No	15	2	PD	2

Number, *M* male, *F* female, *R* right, *L* left, *GTR* gross total resection, *STR* subtotal resection, *RT* external beam radiotherapy, *Gy* gray, *SRS* stereotactic radiosurgery, *HU* hydroxyurea, *PFS* progression free survival, PD progressive disease, *SD* stable disease

ranged from 60 to 100 (median 70) at the time of documented tumor recurrence and initiation of HU therapy. Tumor locations were as follows: frontal ($n = 32$), parietal ($n = 14$), cavernous sinus ($n = 10$), sphenoid wing ($n = 9$), temporal ($n = 8$), tentorial ($n = 4$), cerebellopontine ($n = 2$) and multifocal ($n = 7$) (Table 1).

All patients had been treated previously with surgery in which a complete resection was accomplished in 20 at first resection, partial in 31 and biopsy only in 9 (Table 1). Twenty-nine patients (48%) underwent a second operation [in 4 (6.6%) a third resection] in which repeat tumor histology was consistent with WHO grade 1 meningioma.

All patients had previously been treated with limited-field radiotherapy (adjuvant in 34; at time of first recurrence in 26) (Table 1). In all, conventional fractionated radiotherapy was used in which 1.8–2.0 Gy was administered daily, with a median tumor dose of 54 Gy (range 50.4–55 Gy). Fifty-three patients were in addition treated with stereotactic radiotherapy (adjuvant in 5; at relapse in 48). Stereotactic radiotherapy dose ranged from 12 to 18 Gy (median 14). In all but one patient with multifocal disease (total of seven patients), all lesions were treated with both conventional fractionated radiotherapy and stereotactic radiotherapy.

HU was administered daily and initiated following documentation of tumor progression as demonstrated by neuroradiographic progression (in all patients) or clinical disease progression (in 65% of patients). Median time to initiation of HU following initial surgery was 35 months with a range of 15–132 months. Median time to initiation of HU following radiotherapy (including cyberknife) was 40 months with a range of 15–128 months. A total of 192 cycles of HU were administered. A minimum of one cycle of HU was administered to each patient with a median of 2 cycles (range 1–12). HU was administered at the proscribed dose in all patients (median dose 1500 mg/day; range 1000–2000 mg/day).

Toxicity

Toxicity was retrospectively recorded for all grades for all patients by type using the NCI common toxicity criteria (version 3.0). Table 2 lists all grade 2–5 toxicity observed with each figure representing the sum of the highest grade of toxicity attained, per toxicity, per cycle for all patients. A total of 192 treatment cycles were administered of which there were 6 (10% patients) grade 3 adverse events (AE) and no grade 4 or 5 AE. The most common grade 3 AE was anemia and fatigue (<1% of the total number of HU cycles each). No patient required transfusion nor were there any episodes of neutropenic fever. No treatment-related death occurred. Six patients required a dose reduction (to 1000 mg/day) otherwise all patients were treated at 1000 mg/m^2/day.

Table 2 Hydroxyurea in recurrent WHO grade 1 meningiomas: toxicity

Toxicity	Grade 2	Grade 3	Grade 4	Grade 5	Total
Anemia	6	3	0	0	9
Constipation	8	0	0	0	8
Fatigue	12	3	0	0	15
Infection, without neutropenia	2	0	0	0	2
Lymphopenia	6	0	0	0	6
Nausea	2	0	0	0	2
Neutropenia	5	0	0	0	5
Thrombophlebitis	3	0	0	0	3
Totals	44	6	0	0	50

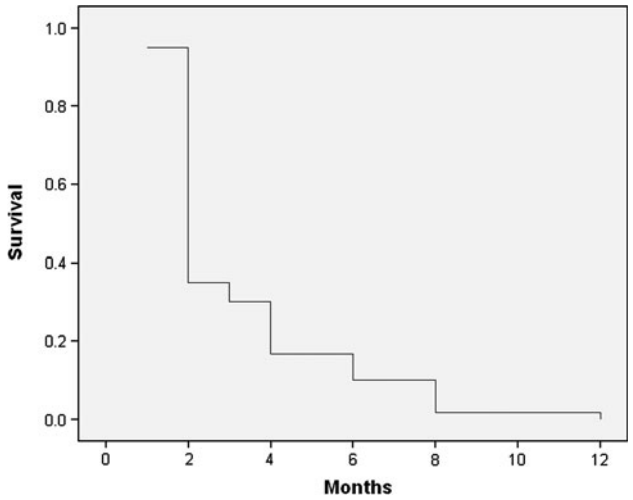

Fig. 1 Progression-free survival in patients with recurrent surgery and radiation refractory WHO grade 1 meningioma treated with hydroxyurea

Response

All patients were assessable for radiographic response and duration of response (Table 1; Fig. 1). Following 1–2 cycles of HU, 39 patients (65%) demonstrated progressive disease. Ten patients (17%) received six or greater cycles of HU. At the conclusion of TMZ, Karnofsky performance status ranged from 50 to 80 with a median of 70 in the entire study group.

No patient (0%) demonstrated a complete or partial response and 21 patients (35%) demonstrated stable disease. Overall median time to tumor progression was 4.0 months (range 3–12 months). Progression free survival at 6- and 12-months was 10% (PFS-6) and 0% (PFS-12).

Forty-eight (80%) patients received an investigational therapy (temozolomide, CPT-11, alpha-interferon or Sandostatin LAR) following progression on HU [21–24].

Discussion

The utility of chemotherapy in the treatment of recurrent meningioma remains ill-defined notwithstanding limited evidence for the use of HU, α-interferon and somatostatin analogues in this setting [12–19, 21, 22]. HU has constituted the primary medical therapy based on several studies and upon the initial report of both in vitro and in vivo activity by Schrell (Table 3) [12, 13]. Schrell demonstrated in vitro that HU, an oral chemotherapy with a variety of anti-tumoral effects, was a potent inhibitor of cultured meningioma cells by inducing apoptosis [12, 13]. Several subsequent clinical trials suggest in vivo efficacy with modest and acceptable toxicity (Table 3). Problematic with the various HU trials however is that many patients had not failed radiotherapy or that radiotherapy was administered concurrently. In the present retrospective study and what arguably is now usual and customary practice in the management of meningiomas, all patients treated with HU had prior radiotherapy as well as histological confirmation of a WHO grade 1 meningioma. In this subset of patients, all previously treated with surgery and radiotherapy and in whom no further surgery or radiotherapy was applicable, there were no radiographic responses, 35% of patients had stable disease and 65% manifested progressive disease following 2 cycles of HU. The duration of stable disease ranged from 3 to 12 months (median 5.0 months). The overall PFS was 10% at 6 months (median PFS 2.0 months). These results in this retrospective case series,

Table 3 Hydroxyurea for recurrent meningioma

Author [References]	# (# benign)	Prior RT	Response (%)	Median TTP (months)	Toxicity (≥grade 3) (%)
Newton et al. [14, 15]	17(13)	7	SD (88)	20	25 (15)
Mason et al. [16]	20 (16)	8	SD (60)	30	5
Rosenthal et al. [17]	15 (5)	1	SD (73)	10	27 (20)
Hahn et al. [18]	21 (4)	21 (concurrent)	SD (52)	14	53 (0)
Loven et al. [19]	12 (8)	6	SD (8)	13	33 (25)

RT radiotherapy, *SD* stable disease, *TTP* time to tumor progression

demonstrate that HU though generally well tolerated and convenient appeared to have very limited activity in recurrent WHO grade 1 meningioma which raises questions of what constitutes effective salvage therapy and indicates an unmet need for alternative treatments for recurrent meningiomas.

At present, there is very limited data regarding outcome measures that best define response to an investigational agent for recurrent meningiomas. As has become customary in brain tumor trials, PFS-6 serves as the endpoint for the majority of trials for recurrent gliomas. A similar strategy has been adopted for recurrent meningiomas, however what constitutes a clinically relevant PFS-6 varies [11, 14–24]. In the imatinib trial, a PFS-6 of 45% was seen in patients with recurrent grade 1 meningiomas and was felt to indicate lack of efficacy [20]. By contrast, in the α-interferon and Sandostatin trials for recurrent meningioma, a PFS-6 of 40% was felt to reflect an active agent [21, 22]. In part these differences reflect prior treatment administered (surgery and radiotherapy) as well as differing interpretations of the meager literature regarding disease progression in treated recurrent meningiomas. In the only randomized placebo controlled trial of patients with recurrent grade 1 meningioma previously treated with radiotherapy (SWOG-9005) were treated with the investigational agent, mifepristone (RU-486), a progesterone antagonist, or placebo. There were 45 subjects for analysis (22 from the treatment arm and 23 on placebo) [11]. Of the 45 patients, 30 died at time of reporting, with a median survival of 31 months (95% confidence interval of 15–50 months). Forty-two of the 45 subjects have progressed with at median time to tumor progression of 6 months (95% confidence interval of 5–7 months). Time to tumor progression was similar in both patients groups (placebo and mifepristone) suggesting mifepristone was an inactive therapy. This study suggests a 50% PFS-6 as a baseline outcome measure from which to compare other medical therapies in similarly treated patients. What has changed in the contemporary management of recurrent meningiomas is the frequent utilization of both fractionated external beam radiotherapy as well as stereotactic radiotherapy [9, 10]. Whether the PFS-6 in the present study (treated with two radiation modalities and surgery) is comparable to that seen in the SWOG-9005 trial (treated with a single radiotherapy modality) is unknown. Regardless, the present may serve as the statistical benchmark for new clinical trials for recurrent meningiomas with targeted agents such as bevacizumab, sunitinib, vatalanib and the somatostatin analogue, pasireotide. A recent phase IIa study (reported only in abstract form) from the Southwest Oncology Group (SWOG S9811) administered HU for recurrent WHO grade 1 meningiomas [26]. All study patients ($n = 29$) were felt not to be candidates for surgery however the number of patients treated with either RT or surgery was not stated. HU at a dose of 20 mg/kg/day resulted in a response rate of 0% and median PFS of 27 months (PFS-3 years 43%). The authors conclude the natural history of meningioma at present is unknown and consequently were uncertain if HU represented an effective cytostatic chemotherapy for recurrent meningioma.

Challenges in treating recurrent meningiomas with targeted and chemotherapeutic agents are several including a lack of interest by the pharmaceutical industry (the most common funding source for cancer clinical trials), minimal interest by neuro-oncology cooperative groups that are predominantly glioma focused, a perception that patients eligible for study are uncommon notwithstanding that meningioma constitutes the most frequent primary brain tumor and a bias by the neuro-oncology community that treatment following failure of surgery and radiotherapy is futile. As a consequence, there are very few open trials for patients with surgery and radiotherapy refractory recurrent meningioma (all comparatively small, single arm Phase 2 studies) attesting to an unmet need in neuro-oncology.

In conclusion though HU is relatively non-toxic and convenient as an orally administered medication with no acute side effects, in patients with recurrent and refractory grade 1 meningiomas, HU appears to have very limited activity in this large retrospective case series.

Conflicts of interest MCC reports participation in advisory board and speaker's bureau for Genentech, MundiPharma, Schering Plough, Sigma Tau. SK Johnston reports no conflicts of interest.

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