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CLINICAL STUDY - PATIENT STUDY

Hydroxyurea for recurrent surgery and radiation refractory high-grade meningioma

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Abstract Hydroxyurea (HU), an orally administered chemotherapy, has become the *de facto* standard chemotherapeutic agent in patients with surgically and radiation refractory meningiomas based on a limited literature. A retrospective case series of 35 patients with recurrent WHO Grade 2 ($n = 22$) or 3 ($n = 13$) meningioma treated with HU following progression after surgery and radiotherapy was collated with primary study objectives of overall response rate, median and progression free survival (PFS) at 6-months. Thirty-five patients (25 women; 10 men: median age 63 years, range 34–86) with recurrent high-grade meningioma were treated with HU (1,000 mg/m^2 orally divided twice per day; one cycle operationally defined as 4 weeks of daily HU). Patients had progressed radiographically after prior therapy with surgery (35/35) and radiotherapy (35/35: external beam radiotherapy 35/35; stereotactic radiotherapy 35/35). No patient received prior chemotherapy or targeted therapy before instituting HU. Patients received 0.5–7 cycles (median 2.0) of HU with modest toxicity (28.5% all grades and 8.5% grade 3+ anemia or fatigue). There were no radiographic responses, 43% of patients had stable disease and 57% manifested progressive disease at first evaluation. The overall PFS was 3.0% at 6 months (median PFS 2.0 months; 95% CI 1.6–2.4). The majority of patients (80%) following progression on HU were subsequently treated on an investigational trial. In this retrospective series, HU though well tolerated and convenient appeared to have very limited activity, raise questions of what constitutes effective salvage therapy and indicates an unmet need for alternative treatments for recurrent high-grade meningiomas.

Keywords Hydroxyurea · Recurrent high-grade meningioma · Surgery and radiation refractory

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Introduction

Meningiomas are the most common intracranial neoplasm constituting 20–30% of all primary brain tumors.[1–7] The World Health Organization (WHO) categorizes meningiomas into three grades; Grade 1 so called benign meningioma; Grade 2 atypical meningioma and Grade 3 anaplastic meningioma. The majority of meningiomas (>80%) are WHO Grade 1 in which complete surgical resection results in prolonged disease free survival or cure. In contrast, WHO 2 and 3 (high-grade) meningiomas despite initial surgical resection often accompanied by radiotherapy frequently recur and require re-treatment primarily with re-resection or re-irradiation. A subset of recurrent high-grade meningiomas are surgery and radiation refractory and in clinically appropriate patients', systemic therapy is often considered and administered. At present however there exist a limited number of available systemic therapies [1, 2, 4, 5, 7]. The Central Nervous System (CNS) National Comprehensive Cancer Network (NCCN) guidelines, based on consensus expert opinion, suggests as treatment options hydroxyurea, α-interferon or Sandostatin LAR, a somatostatin inhibitor [8]. These recommendations however are based upon a comparatively small literature

treating patients with surgery and radiation refractory meningiomas [9–28]. Similar to a prior report in concept and design, this retrospective case series determined progression free survival in 35 adult patients with recurrent high-grade meningiomas treated with the orally administered chemotherapy, hydroxyurea (HU), following progression after prior surgery and radiotherapy [26].

Patients and methods

A retrospective case series of patients all treated by the author with WHO Grade 2 or 3 recurrent meningiomas following prior surgery and radiotherapy treated with HU between 1/2000 and 12/2010. Approval for the retrospective analysis was obtained from all relevant university human investigation committees. Consent for treatment was obtained from each subject after disclosing the potential risks of HU and discussion of potential alternative treatment including no treatment.

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 2 or 3 meningiomas. The primary end point was progression free survival (median and 6-month).

Patient selection

Patients had histologically proven WHO Grade 2 or 3 meningioma that was recurrent neuroradiographically. All patients had pro-gressed following conventional external beam and stereotactic radiothera-py (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 to minimize early RT injury patterns. Patients had radiographi-cally measurable disease by cranial contrast-enhanced magnetic resonance imaging (MR). Histological confirmation of tumor recurrence was not required. Pregnant or lactating women were not treated. Patients of child bearing potential were asked to implement contra–ceptive measures during HU chemotherapy. 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. Patients could not have an active concomitant malignancy except skin cancer (squamous cell or basal cell).

Drug schedule

As outlined in a prior report, hydroxyurea (HU; Hydrea; Bristol-Myers-Squibb, NY) was administered orally for 28-consecutive days (1,000 mg/m^2/single daily dose) every 4-weeks (operationally defined as a cycle of therapy) [9–16, 26]. HU was obtained commercially and billed to third party payers. No pharmaceutical sponsorship was provided in the conduct of this retrospective study. Every 8 weeks and following two cycles of HU, patients were re-evaluated with contrast cranial MR. Patients continued HU treatment if clinically and radiographically stable or improved. Subsequent clinical and neuroradiographic evaluations were every other month. Alternative meningioma-directed therapy (or no therapy) was offered to patients that radiographically progressed. Complete blood counts and neurologic examination were obtained on day 1 of each 28-day HU cycle. Concurrent medications were utilized and included non-enzyme inducing anticonvulsants (24 patients), narcotics (12 patients), dexamethasone (18 patients), anti-constipation medication (14 patients) and anticoagulants (4 patients).

No premedication was required with oral HU. Treatment with HU was repeated every 28 days 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 4.0).

Concurrent dexamethasone was used for control of neurologic signs and symptoms. Oral dexamethasone was used concurrently in 18 patients and was added to eight patients with clinical disease progression. Dexamethasone dose was decreased in six patients as patient clinical status permitted.

Method of evaluation

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 MR was performed after every two cycles of HU (i.e. every 8 weeks) as previously reported [26]. Modified neuroradiographic response criteria as defined by Macdonald were used [29–30].

In patients with radiographic stable disease, partial response or complete response, two additional cycles of

HU was adminis-tered and repeat MRI was obtained. 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.

Progression free survival (PFS) and overall survival (OS) were defined as the time from the 1st day of treatment with HU until progression or death (PFS) or death (OS). Patients discontinued HU if there was progressive disease, development of unacceptable toxicity, patient refusal or noncompliance with treatment.

Results

Study population

Thirty-five patients (25 women; 10 men) ages 34–86 years (median 63), with recurrent WHO Grade 2 ($n = 22$) or Grade 3 ($n = 13$) meningioma (original pathology reviewed and confirmed in all cases) previously treated with surgery and RT were treated with HU (Table 1). Patients with recurrent Grade 2 or 3 meningioma treated with HU and not refractory to surgery and RT were not included in this retrospective study. Recurrent meningioma was defined by objective neuroradiographic progression (>25% increase in tumor size) as compared with prior baseline neuroradiographic images. All neuroradiography was reviewed by a neuroradiologist blinded to treatment and by the treating neuro-oncologist. All patients underwent cranial MR demonstrating progressive disease within 2 weeks of HU administration.

Patients presented at the time of tumor recurrence with the following signs and symptoms: worsening hemiparesis ($n = 20$), increased seizures ($n = 16$), headache ($n = 14$), gait disturbance ($n = 8$), and ophthalmoplegia ($n = 6$). Patient performance status using the Karnofsky scale 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 ($n = 19$), parietal ($n = 7$), cavernous sinus ($n = 5$), temporal ($n = 3$), sphenoid wing ($n = 5$), tentorial ($n = 3$), cerebellopontine ($n = 1$) and multifocal ($n = 5$) (Table 1).

All patients had been treated previously with surgery in which a complete resection was accomplished in 17 at first resection, partial in 13 and biopsy only in 5 (Table 1). Twenty-one patients (60%) underwent a second operation (in 2 [5.7%] a third resection) in which repeat tumor histology was consistent with a WHO Grade 2 or 3 meningioma.

All patients had previously been treated with limited-field radiother-apy (adjuvant in 35) (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 60 Gy (range 59.4–60 Gy). Thirty-five patients were in addition treated with stereotactic radiotherapy, all at relapse. Stereotactic radiotherapy dose ranged from 12 to 18 Gy (median 14). All patients 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 60% of patients). Median time to initiation of HU following initial surgery was 30 months with a range of 12–62 months. Median time to initiation of HU following stereotactic radiotherapy was 6 months with a range of 3–12 months. A total of 88.5 cycles of HU were administered. A minimum of one cycle of HU was administered to each patient with a median of two cycles (range 0.5–7). HU was administered at the prescribed dose in all patients. No other anti-meningioma agents aside from dexamethasone were utilized during HU treatment.

Toxicity

Toxicity was retrospectively recorded for all grades for all patients by type using the NCI common toxicity criteria (version 4.0). Table 2 lists all Grade 2–3 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 88.5 treatment cycles were administered of which there were 3 (8.5% patients) grade 3 adverse events (AE). No grade 4 or 5 AE were observed. 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. Five patients required a dose reduction (to 1,000 mg/day) otherwise all patients were treated at 1,000 mg/m^2/d (Fig. 1)

Response

All patients were assessable for radiographic response and duration of response (Table 1; Fig. 1). Following two cycles of HU, 20 patients (57%) demonstrated progressive disease. Six patients (17%) received four or greater cycles of HU. At the conclusion of HU, Karnofsky performance status ranged from 40 to 80 with a median of 70 in the entire study group.

No patient (0%) demonstrated a complete or partial response and 21 patients (43%) demonstrated stable disease. Median and range of progression free survival was 2.0 months [95% CI 1.6–2.4] and 0.5–7 months, respectively. Progression free survival at 6- (PFS-6) and

Table 1 Patient treatment characteristics

#	Gender/ Age	Location	Initial therapy			Salvage therapy			HU therapy		
			Surgery	RT (Gy)	SRS	Surgery	RT (Gy)	SRS (Gy)	# cycles	Response	PFS
1	f/86	L frontal	GTR	60	No	No	No	15	0.5	PD	0.5
2	m/75	R frontal	STR	59.4	No	STR	No	14	0.5	PD	0.5
3	f/70	R cavernous sinus, R sphenoid wing	STR	54	No	STR	No	12	0.5	PD	0.5
4	f/68	L frontal	GTR	60	No	STR	No	14	1	PD	1
5	f/56	R parietal	GTR	60	No	STR	No	15	1	PD	1
6	f/73	R sphenoid wing	STR	60	No	No	No	15	1	PD	1
7	m/42	R temporal, R frontal	STR	60	No	STR x2	No	14	1	PD	1
8	f/61	L tentorium/Cerbellopontine angle	GTR	60	No	STR x1	No	14	1	PD	1
9	f/58	R sphenoid wing	STR	60	No	No	No	15	1	PD	1
10	f/80	R Frontal	GTR	60	No	STR	No	14	1.5	PD	1.5
11	m/52	L frontal	GTR	59.4	No	GTR	No	15	1.5	PD	1.5
12	f/66	R frontal, parietal	STR	60	No	STR	No	16	1.5	PD	1.5
13	f/67	L temporal	GTR	60	No	STR	No	15	1.5	PD	1.5
14	m/68	R cavernous sinus	Biopsy	60	No	No	No	12	2	PD	2
15	m/51	R frontal, R parietal	STR	59.4	No	STR x2	No	15	2	PD	2
16	f/78	R frontal	GTR	60	No	No	No	12	2	PD	2
17	f/63	L frontal	GTR	60	No	STR	No	14	2	PD	2
18	f/69	R temporal	GTR	59.4	No	GTR	No	15	2	PD	2
19	f/66	L and R frontal	STR	60	No	No	No	14	2	PD	2
20	m/50	R parietal	Biopsy	59.4	No	No	No	18	2	PD	2
21	f/40	L frontal	GTR	60	No	No	No	18	2.5	SD	2.5
22	f/63	R tentorium	GTR	59.4	No	STR	No	14	2.5	SD	2.5
23	f/62	R Cavernous sinus	Biopsy	60	No	No	No	18	3	SD	3
24	f/48	R Frontal	GTR	60	No	STR	No	14	3	SD	3
25	m/63	R Parietal	STR	59.4	No	No	No	18	3	SD	3
26	f/60	L frontal and parietal	Biopsy	60	No	No	No	14	3.5	SD	3.5
27	f/76	L and R frontal	STR	59.4	No	No	No	12	3.5	SD	3.5
28	f/64	R tentorium	GTR	59.4	No	STR	No	14	4	SD	4
29	f/79	R frontal	GTR	60	No	STR	No	15	4	SD	4
30	f/70	R frontal	GTR	59.4	No	GTR	No	15	4.5	SD	4.5
31	m/34	R frontal-parietal	GTR	60	No	GTR	No	14	4.5	SD	4.5
32	f/38	R cavernous sinus	Biopsy	59.4	No	No	No	15	5	SD	5
33	f/82	R temporal, falx, sphenoid wing	STR	60	No	STR	No	14	5	SD	5
34	f/62	L cavernous sinus, L sphenoid wing	STR	59.4	No	No	No	14	6	SD	6
35	f/47	L and R frontal	STR	No	No	STR	No	12	7	SD	7

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

12-months (PFS-12) was 3.0 and 0%. Median survival following initiation of HU was 8 months (10 months for WHO Grade 2 meningiomas and 6 months for WHO Grade 3 meningiomas).

Thirty (86%) patients received an investigational therapy (temozolomide, CPT-11, alpha-interferon or Sandostatin LAR) following progression on HU.

Discussion

A challenge in considering systemic therapy for recurrent surgery and radiation refractory high-grade meningioma is the paucity of clinical trials from which to base treatment [9–28]. There is a small study of high-grade meningiomas treated following initial surgery with a sarcoma adjuvant

Table 2 Hydroxyurea in recurrent WHO grade 2/3 (meningiomas: toxicity)

Toxicity	Grade 2	Grade 3	Total
Anemia	4	1	5
Constipation	6	0	6
Fatigue	10	2	12
Infection, without neutropenia	2	0	2
Lymphopenia	5	0	5
Nausea	2	0	2
Neutropenia	3	0	3
Thrombophlebitis	2	0	2
Totals	34	3	37

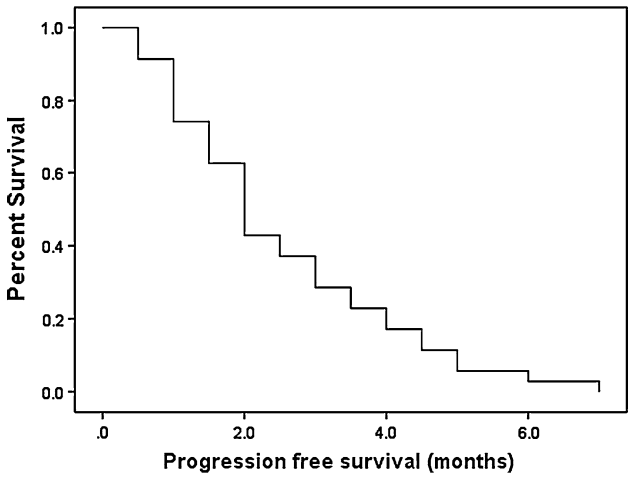

Fig. 1 Kaplan–Meier plot of progression free survival for recurrent high grade meningioma treated with hydroxyurea

chemotherapy regimen (cyclophosphamide, adriamycin and vincristine: CAV), but without a radiotherapy only control arm it is unclear what the contribution of CAV was to upfront radiotherapy. At present there is no compelling data to suggests activity of cytotoxic chemotherapy in the treatment of high-grade meningioma, either in the up-front setting or at recurrence [1, 2, 4, 5, 7, 26, 28]. In addition, the majority of systemic therapy trials in recurrent meningioma are comprised of small numbers of patients often not stratified with respect to prior treatment or WHO tumor grade. Table 3 summarizes the use of HU for recurrent high-grade meningioma and illustrates the limited literature available [11–16, 26]. Patients in these studies utilizing HU were not stratified with respect to tumor grade in that of 85 patients treated with HU, 39 (46%) had high-grade meningiomas. Additionally, prior treatment varied and in the majority of patients, radiotherapy had not been administered (22/85; 26%) or was administered concurrently (21; 25%). Consequently assessing response to HU as a single agent is problematic. Contemporary treatment of high-grade meningioma entails resective surgery, often more than one, as well as radiotherapy. Radiotherapy treatment of high-grade meningioma increasingly utilizes both fractionated external beam radiotherapy and stereotactic radiation, typically administered at differing times during the treatment history. The CNS NCCN guidelines recommend fractionated external beam radiotherapy following initial surgery for high-grade meningiomas and further suggest stereotactic radiation at recurrence [8]. This treatment approach was applied in this retrospective case series as all patients underwent surgery (100% 1 surgery; 60% 2 surgeries; and 6% 3 surgeries) and radiotherapy (100% fractionated external beam radiotherapy; 100% stereotactic radiation) before treatment with HU. Though toxicity from HU was modest (8.5% Grade 3 AE and no Grade 4 or 5 AE), there were no radiographic responses (best response stable disease in 43%) and all responses were of short duration (median PFS 2.0 months; PFS-6 3%). This contemporary retrospective study therefore suggests HU has a very limited role in the treatment of surgery and radiation refractory high-grade meningioma.

A number of small studies utilizing targeted therapy for recurrent high-grade meningioma have been reported (Table 4) [17–24, 26]. Of the 117 patients evaluated and reported to date, most striking have been studies employing targeted agents directed against the vascular endothelial growth factor (VEGF) signaling pathway, a pathway recognized to be up-regulated in meningiomas [17–19]. Two anti-VEGF approaches have been utilized, VEGF ligand directed therapy (bevacizumab) and VEGF receptor (VEGFR) directed therapy (sunitinib, vatalanib). A larger prospective phase two study of bevacizumab has recently opened and likely will determine if this approach for both recurrent WHO Grade 1 and high-grade meningioma has merit. Neither the sunitinib or vatalanib trial (VEGFR inhibitors) has been reported in a peer reviewed manuscript; consequently it is premature to draw conclusions as to efficacy and importantly for this class of agents, associated toxicity given that these targeted agents are cytostatic and likely will require low term usage.

Defining activity for an anti-meningioma agent has been problematic again due to a limited literature with few prospective trials treating patients in a similar manner as mentioned above. The establishment of survival metrics that defines an active anti-meningioma agent has not been universally agreed upon [1, 20–27]. By example, the imatinib and erlotinib meningioma trials have reported as negative notwithstanding similar results to that in another study purportedly positive study, i.e. Sandostatin LAR [20–22, 24, 26]. In part these differences reflect prior treatment administered (surgery and radiotherapy) as well as differing interpretations of the meager literature regarding treatment of recurrent meningiomas. In the only

Table 3 Hydroxyurea for recurrent meningioma (adapted from [26])

Author	# (# Grade 2/3)	Prior RT	Response (%)	Median TTP (mns)	Toxicity (≥Grade 3) (%)
Newton et al. [11, 12]	17 (4)	7	SD (88)	20	25 (15)
Mason et al. [13]	20 (4)	8	SD (60)	30	15
Rosenthal et al. [14]	15 (10)	1	SD (73)	10	27 (20)
Hahn et al. [15]	21 (17)	21 (concurrent)	SD (52)	14	53 (0)
Loven et al. [16]	12 (4)	6	SD (8)	13	33 (25)

RT Radiotherapy, *SD* Stable disease, *TTP* Time to tumor progression, *mns* months

Table 4 Targeted therapy for recurrent high-grade meningioma (adapted from [26])

Inhibitor [Reference]	Target	Number of patients	Radiographic response rate (%)	Progression free survival	
				Median	6-month
Bevacizumab [17]	VEGF	6	0	4.0 mns	NS
Sunitinib [18]	VEGFR	30	0	5.1 mns	36%
Vatalanib [19]	VEGFR	21	5.8	3.65 mns	37.5%
Imatinib [20, 21]	PDGFR	10	0	2.0 mns	29.4%
Erlotinib [22]	EGFR	25	0	2.0 mns	25%
Pasireotide [23]	sst	17	0	4.0 mns	12%
Sandostatin LAR [24]	sst	8	25	3.0 mns	25%

VEGF vascular endothelial growth factor, *VEGFR* vascular endothelial growth factor receptor, *PDGFR* platelet derived growth factor receptor, *EGFR* epidermal growth factor receptor, *sst* somatostatin receptor, *Mns* months, *NS* not stated

randomized placebo controlled trial of patients with recurrent Grade 1 meningioma previously treated with radiotherapy (SWOG-9005) and evaluating the investigational agent, mifepristone (RU-486), a progesterone antagonist, there were 45 subjects for analysis (22 from the treatment arm and 23 on placebo) [27]. Time to tumor progression was similar in both patients groups (placebo and mifepristone) suggesting mifepristone was an inactive therapy. As well the 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 as mentioned is the frequent utilization of both fractionated external beam radiotherapy as well as stereotactic radiotherapy. In a recent study of HU treated recurrent surgery and radiation refractory WHO Grade 1 meningioma ($n = 60$), PFS-6 was 10% suggesting a more contemporary baseline to which to compare medical therapies [26]. A similar study of high-grade meningiomas has not been performed though arguably the present study suggests that HU is inactive with a PFS-6 of 3% and consequently may be representative of a natural history study of recurrent surgery and radiotherapy refractory high-grade meningioma. Nonetheless other authors contend that an active agent for recurrent high-grade meningioma is defined by a PFS-6 of 30% [20–23]. These studies demonstrate a need for consensus with respect definitions of anti-meningioma activity as defined by PFS-6 to permit comparisons between studies.

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), very modest 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 perception 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 high-grade meningiomas, HU appears to have very limited activity in this comparatively large retrospective case series.

Conflict of interest The author reports no conflict of interest or financial disclosure related to this article.

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