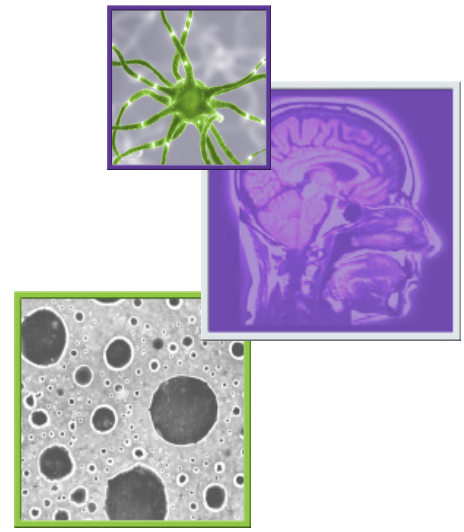
CASE SERIES

IFN-α for recurrent surgery- and radiation-refractory high-grade meningioma: a retrospective case series



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Practice Points

- Literature regarding systemic therapy for recurrent high-grade meningioma refractory to surgery and radiotherapy is sparse.
- The National Comprehensive Cancer Network (NCCN) guidelines commend hydroxyurea, IFN-α and somatostatin analogs (i.e., Sandostatin® LAR; Novartis, NJ, USA) as systemic therapies for recurrent meningioma.
- In this retrospective study, 35 patients with recurrent high-grade meningioma who had failed prior surgery and radiotherapy were treated with IFN-α. Progression-free survival (median: 12 weeks) and overall survival suggested modest activity for this regimen (5×10^6 units subcutaneously administered three times per week every week).
- Toxicity of IFN-α was moderate, with 20% of patients sustaining grade 3 toxicity, which manifested primarily as fatigue.
- IFN-α appears to be a reasonable systemic therapeutic option for patients with recurrent meningioma.

SUMMARY **Aim:** Limited literature is available regarding the treatment of recurrent surgery- and radiation-refractory meningioma, and it primarily examines the treatment of low-grade (WHO grade 1) meningioma. Data regarding systemic therapy for recurrent high-grade meningioma are sparse. A retrospective case series of patients with recurrent WHO grade 2/3 meningioma treated with IFN-α following progression after surgery, radiotherapy and hydroxyurea was carried out, with the primary study objective of overall response rate, and median and 6-month progression-free survival (PFS). **Patients & methods**: 35 patients (28 women and 17 men; median age 63 years; range: 36–86 years) with recurrent high-grade meningioma (WHO grade 2 [n = 22] or 3 [n = 13]) were treated with IFN-α (10 million units/m^2) subcutaneously every 2 days; one cycle was operationally defined as 4 weeks of IFN-α. Patients had progressed radiographically after prior therapy with surgery (35 out of 35), radiotherapy (35 out of 35; external-beam radiotherapy: 35 out of 35; and stereotactic radiotherapy: 34 out of 35) and hydroxyurea chemotherapy (35 out of 35). One patient was also treated with a somatostatin analog before initiating IFN-α treatment. **Results**: Patients received one to 13 cycles (median: three) of IFN-α with moderate toxicity (100% of patients manifested grades 1–3 toxicity, of which only 20% were grade 3). There

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were no radiographic responses, 63% of patients had stable disease and 37% manifested progressive disease at first evaluation. PFS was 17% at 6 months (95% CI: 0.07–0.31; median PFS: 12 weeks; 95% CI: 8–20 weeks; range: 4–52 weeks). Following progression on IFN-α, the majority of patients (60%) were subsequently treated on an alternative therapy. **Conclusion**: In this large retrospective series, IFN-α was moderately toxic, but appeared to have limited activity in patients with recurrent high-grade meningiomas.

Meningiomas are the most common intracranial neoplasm, constituting 20–30% of all primary brain tumors [1–6]. WHO categorizes meningiomas into three grades: grade 1, so called benign meningiomas; grade 2, atypical meningiomas; 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 [1–6]. By contrast, despite initial surgical resection, WHO grade 2 and 3 (high-grade) meningiomas, often accompanied by radiotherapy (RT), frequently recur and require retreatment primarily with reresection or reirradiation. 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, a limited number of available systemic therapies exist [7–12]. The CNS National Comprehensive Cancer Network (NCCN) guidelines, based on consensus expert opinion, suggest hydroxyurea, IFN-α (Schering-Plough Pharmaceuticals, NJ, USA) or Sandostatin® LAR (Novartis, NJ, USA), a somatostatin agonistic analog as treatment options [7]. These recommendations, however, are based upon a comparatively small number of studies treating patients with surgery- and radiation-refractory meningioma and primarily WHO grade 1 meningioma [7–12]. Similar to a prior report, this retrospective case series of 35 adult patients determined progression-free survival (PFS) in patients with recurrent high-grade meningiomas treated with IFN-α following progression after previously surgery and RT [11].

Patients & methods

In this retrospective case series, patients with WHO grade 2 (n = 22) or 3 (n = 13) recurrent meningioma were treated with IFN-α between January 2000 and December 2012. Approval for the retrospective analysis was obtained from the universities (University of Southern California, CA, USA; Moffitt Cancer Center, FL, USA; and University of Washington, WA, USA) Human Investigation Committees. Consent for treatment was obtained from each subject after disclosing the potential risks of IFN-α and discussing the potential alternative treatments, including no treatment. IFN-α was obtained commercially and billed to third-party payers. No pharmaceutical sponsorship was provided in the conduct of this retrospective study.

Objectives & end points

The two primary objectives of this retrospective study were determination of the efficacy and toxicity of IFN-α in the treatment of adults with surgery- and radiation-refractory recurrent WHO grade 2 or 3 meningiomas. The primary end point was 6-month PFS (PFS-6).

Patient selection

Patients had histologically proven WHO grade 2 or 3 meningiomas that were recurrent neuroradiographically. All patients had progressed following definitive RT and surgery, and were not considered eligible for further RT or surgery (Table 1). All patients were previously treated with hydroxyurea and manifested disease progression (Table 1). At least 3 months had elapsed since prior RT. Patients had radiographically measurable disease, wherein recurrent tumor was bidimensionally measurable (at least 1.0 × 1.0 cm) by cranial contrast-enhanced MRI. Histological confirmation of tumor recurrence was not required. Pregnant and lactating women were not treated. Patients of child-bearing potential were asked to implement contraceptive measures during IFN-α 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 IFN-α therapy.

Drug schedule

IFN-α was administered to all patients at a dose of 10 million units/m^2 subcutaneously every 2 days [11]. A cycle of therapy was defined as 4 weeks. Treatment cycles were repeated every

Table 1. Meningioma patient treatment characteristics.

Patient number	Sex/age (years)	Location	Initial therapy			Salvage therapy				IFN-α therapy		
			Surgery	RT (Gy)	SRS (Gy)	Surgery	RT (Gy)	SRS (Gy)	Chemotherapy (cycles)	Cycles (n)	Response	PFS (weeks)
1†‡	F/86	L frontal	GTR	60	No	No	No	15	HU (1)	1	PD	4
2†	M/75	R frontal	STR	59.4	No	STR	No	14	HU (1)	2	PD	8
3†	F/70	R cavernous sinus, R sphenoid	STR	54	No	STR	No	12	HU (1)	6	SD	26
4†‡	F/68	L frontal	GTR	60	No	STR	No	14	HU (1)	4	SD	16
5	F/63	L and R parietal	STR	54	No	STR	No	15	HU (1) Sandostatin® LAR (3)	13	SD	52
6‡	F/72	L sphenoid, L cavernous sinus	STR	60	No	Biopsy	No	12	HU (1)	3	SD	12
7†	F/56	R parietal	GTR	60	No	STR	No	15	HU (1)	2	PD	8
8†‡	M/42	R temporal, R frontal	STR	60	No	STR × 2	No	14	HU (1)	3	PD	12
9†	F/61	L tentorium, L cerebello-pontine angle	GTR	60	No	STR	No	14	HU (1)	5	SD	20
10‡	M/36	Bifrontal	STR	60	No	No	No	14	HU (3)	2	PD	8
11	F/63	L parietal, R parietal, L occipital	STR	54	No	STR	No	15	HU (2)`	3	PD	12
12†	F/80	R frontal	GTR	60	No	STR	No	14	HU (1.5)	2	PD	8
13†	M/52	L frontal	GTR	59.4	No	GTR	No	15	HU (1.5)	7	SD	28
14†‡	F/66	R frontal, R parietal	STR	60	No	STR	No	16	HU (1.5)	3	PD	12
15	F/82	L sphenoid, L pterygo-palatine fossa, L cavernous sinus	STR	60	No	No	No	12	HU (2)	5	SD	20
16†	F/67	L temporal	GTR	60	No	STR	No	15	HU (1.5)	6	SD	24
17†‡	M/68	R cavernous sinus	Biopsy	60	No	No	No	12	HU (2)	4	SD	16
18†	M/51	R frontal, R parietal	STR	59.4	No	STR × 2	No	15	HU (2)	7	SD	28
19†	F/78	R frontal	GTR	60	No	No	No	12	HU (2)	2	PD	8
20†‡	F/63	L occipital	GTR	60	No	STR	No	14	HU (2)	3	SD	12
21†	F/69	R frontal	GTR	59.4	No	GTR	No	15	HU (2)	5	SD	20
22†	F/66	L frontal, R frontal	STR	60	No	No	No	14	HU (2)	6	SD	24
23†‡	F/40	R parietal	GTR	60	No	No	No	18	HU (2.5)	8	SD	32
24†	F/66	R tentorium	GTR	59.4	No	STR	No	14	HU (2.5)	1	PD	4
25†	F/62	R cavernous sinus	Biopsy	60	No	No	No	14	HU (3)	5	SD	20

†Previously reported in part [12,16].
‡WHO grade 3 meningioma.
F: Female; GTR: Gross total resection; HU: Hydroxyurea; L: Left; M: Male; PD: Progressive disease; PFS: Progression-free survival; R: Right; RT: External-beam radiotherapy; SD: Stable disease; SRS: Stereotactic radiosurgery; STR: Subtotal resection.

Table 1. Meningioma patient treatment characteristics (cont.).

Patient number	Sex/age (years)	Location	Initial therapy			Salvage therapy				IFN-α therapy		
			Surgery	RT (Gy)	SRS (Gy)	Surgery	RT (Gy)	SRS (Gy)	Chemotherapy (cycles)	Cycles (n)	Response	PFS (weeks)
26†‡	F/48	R frontal	GTR	60	No	STR	No	14	HU (3)	11	SD	44
27†	M/66	R parietal	STR	59.4	No	No	No	18	HU (3)	1	PD	4
28†‡	F/60	L fontal, L parietal	Biopsy	60	No	No	No	14	HU (3.5)	4	SD	16
29†	F/76	L and R frontal	STR	59.4	No	No	No	12	HU (3.5)	1	PD	4
30†	F/79	R frontal	GTR	60	No	No	No	15	HU (4)	2	PD	8
31†	F/70	R frontal	GTR	59.4	No	GTR	No	15	HU (4.5)	2	PD	8
32†‡	F/38	R cavernous sinus	Biopsy	59.4	No	No	No	15	HU (15)	8	SD	32
33†	F/82	R temporal, falx, R sphenoid	STR	60	No	STR	No	14	HU (5)	1	PD	4
34†‡	F/62	L cavernous sinus, L sphenoid	STR	59.4	No	No	No	14	HU (6)	5	SD	20
35†	F/67	L and R frontal	STR	54	No	STR	No	12	HU (7)	2	PD	8

†Previously reported in part [12,16].
‡WHO grade 3 meningioma.
F: Female; GTR: Gross total resection; HU: Hydroxyurea; L: Left; M: Male; PD: Progressive disease; PFS: Progression-free survival; R: Right; RT: External-beam radiotherapy; SD: Stable disease; SRS: Stereotactic radiosurgery; STR: Subtotal resection.

4 weeks, provided that all hematologic toxicity from the previous cycle had resolved to grade 2 or less, and all nonhematologic toxicity had resolved to grade 1 or less. No dose escalations were permitted. Dose reduction for toxicity was allowed in 50% increments. All toxicities, including hematologic, due to IFN-α therapy were rated retrospectively according to the NIH Common Toxicity Criteria (version 4.0) [13].

Concurrent dexamethasone was permitted for control of neurologic signs and symptoms. Oral dexamethasone was used in 16 patients. In eight patients, the dose was increased due to disease progression, which was demonstrated clinically and neuroradiographically. In five patients, a stable dexamethasone dose was maintained. Anticonvulsant drugs were permitted and were used in 20 patients.

Method of evaluation

Blood counts were obtained on day 1 of each IFN-α cycle (or more often if clinically indicated), neurologic examination was performed every 4 weeks and contrast-enhanced MRI was performed after every two cycles of IFN-α (i.e., every 8 weeks) as previously reported [14]. Modified neuroradiographic response criteria as defined by Macdonald *et al.* were used [14].

In patients with radiographic stable disease, partial response or complete response, two additional cycles of IFN-α were administered and a repeat MRI was obtained. Patients were continued on IFN-α therapy until documentation of progressive disease, at which point patients discontinued IFN-α and were either monitored or offered alternative therapy.

PFS and overall survival (OS) were defined as the time from day 1 of treatment with IFN-α until progression (PFS) or death (OS). Patients discontinued IFN-α if there was progressive disease, development of unacceptable toxicity, patient refusal or noncompliance with treatment. The PFS and OS function was estimated by the Kaplan–Meier product limit method, with a 95% CI based on the log hazard.

Results

Study population

Thirty five patients (25 women; 10 men) aged 34–86 years (median 63 years), with recurrent WHO grade 2 (n = 22) or 3 (n = 13) meningioma (original pathology reviewed and confirmed in all cases) were treated with IFN-α (Table 1). Recurrent meningioma was defined by objective neuroradiographic progression (>25% increase in the product of the orthogonal diameters) as compared with prior baseline neuroradiographic images. All neuroradiography was reviewed by a neuroradiologist blinded to treatment and by the treating neuro-oncologist.

Patients presented at the time of tumor recurrence with the following signs and symptoms: worsening hemiparesis (n = 18); increased seizures (n = 14); headache (n = 13); gait disturbance (n = 10); and ophthalmoplegia (n = 8). Patient performance status using the Karnofsky Performance Status scale ranged from 60 to 100 (median 70) at the time of documented tumor recurrence and initiation of IFN-α therapy. Tumor locations were as follows: frontal (n = 18); parietal (n = 8); cavernous sinus (n = 7); temporal (n = 4); sphenoid wing (n = 4); tentorial (n = 2); cerebellopontine (n = 1); and multifocal (n = 10) (Table 1). Contrast-enhancing tumor size in the brain, as determined by modified Macdonald criteria (product of the orthogonal diameters), ranged from 7 to 45 cm^2 (median: 12 cm^2). All patients underwent octreotide nuclear medicine imaging before administration of IFN-α and evidence of distant metastases was seen in two patients (lung metastases).

All patients had been treated previously with surgery in which a complete resection was accomplished in 15 patients at first resection, partial in 16 and a biopsy in four (Table 1). Twenty one patients (60%) underwent a second operation and two patients (5.7%) had 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 RT (adjuvant in 35) (Table 1). Conventional fractionated RT was used in all patients in which 1.8–2.0 Gy was administered daily, with a median tumor dose of 60 Gy (range: 54–60 Gy). Thirty five patients were treated with stereotactic RT, all at relapse. Stereotactic RT dose ranged from 12 to 18 Gy (median: 14). Overall, all 35 patients were treated with both conventional fractionated RT and stereotactic RT.

IFN-α was administered three times per week 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 IFN-α following initial surgery was 30 months, with a range of 12–62 months. Median time to initiation of IFN-α following RT, including stereotactic RT, was 6 months, with a range of 3–12 months. A total of 144 cycles of IFN-α were administered. A minimum of one cycle of IFN-α was administered to each patient with a median of three cycles (range: 1–13). IFN-α was administered at the prescribed dose in all patients. No other antimeningioma agents, apart from dexamethasone and anticonvulsant drugs, were utilized during IFN-α treatment.

Toxicity

Toxicity was retrospectively recorded in all of the patients for all grades of meningioma by type using the National Cancer Institute common toxicity criteria (version 4.0) [13]. 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 144 treatment cycles were administered, of which there were 15 grade 3 adverse events (AEs) in seven (20%) patients. No grade 4 or 5 AEs were observed. The most common grade 3 AEs were anemia (10%) and fatigue (10%; of the total number of IFN-α cycles). No patient required transfusion and there were no episodes of neutropenic fever. No treatment-related deaths occurred. Only six patients (17%) required a dose reduction (5 million units/m^2/dose), otherwise all patients were treated at 10 million units/m^2 every other day. No patients discontinued therapy due to toxicity.

Response

All patients were assessable for radiographic response and duration of response (Table 1). Following one cycle of IFN-α, five patients (14%) demonstrated progressive disease. Following two cycles of IFN-α treatment, eight patients (23%) demonstrated progressive disease. Nine patients (26%) received six or more cycles of IFN-α. At the end of IFN-α, Karnofsky Performance Status ranged from 40 to 80 with a median of 60 for the entire study group.

There were no radiographic responses, 63% of patients had stable disease and 37% manifested progressive disease at first evaluation.

Table 2. IFN-α in recurrent WHO grade 2/3 meningioma.

Toxicity	Grade 2 (n)	Grade 3 (n)	Total (n)
Anemia	4	4	8
Constipation	6	0	6
Fatigue	10	4	14
Infection, without neutropenia	2	2	4
Lymphopenia	5	2	7
Nausea	2	0	2
Neutropenia	3	2	5
Thrombophlebitis	2	1	3
Total	34	15	49

PFS was 17% at 6 months (95% CI: 0.07–0.31; median PFS: 12 weeks; 95% CI: 8–20 weeks; range: 4–52 weeks). Median OS from initiation of IFN-α ranged from 2 to 16 months (median: 5 months; 95% CI: 3–14 months) Figure 1. Twenty one (60%) patients received an investigational therapy (e.g., temozolomide, CPT-11, IFN-α or Sandostatin LAR) following progression on IFN-α. Median survival following the administration of IFN-α was 3 months (95% CI: 1–4 months; range: 1.5–6 months).

Discussion & conclusion

A challenge in considering systemic therapy for recurrent surgery- and radiation-refractory high-grade meningioma is the paucity of clinical trials on which to base treatment (Table 3) [15–27]. There has been one small study of high-grade meningiomas that were treated following initial surgery with a sarcoma adjuvant chemotherapy regimen (cyclophosphamide, adriamycin and vincristine); however, the trial had no control arm (e.g., surgery plus RT only) and, consequently, it is uncertain, based on this trial, if adjuvant chemotherapy has a role in newly diagnosed high-grade meningioma [15]. Currently, and as espoused in the CNS NCCN guidelines, there are no compelling data that demonstrate activity of cytotoxic chemotherapy in the treatment of newly diagnosed high-grade meningioma [7]. More problematic, however, is recurrent high-grade meningioma that has progressed despite administration of both surgery and RT.

Hydroxyurea, one of three agents recommended in the CNS NCCN guidelines, was recently shown to have no activity (median PFS and 6-month PFS were 2 months and 3%, respectively) as a single modality of therapy in patients with surgery- and radiation-refractory high-grade meningioma [16]. As shown in the current study, all patients (some admittedly reported previously) had been treated with hydroxyurea and rapidly progressed (Table 1). Therefore, alternative non-protocol therapies for the current study's patients were treatment with either IFN-α or Sandostatin LAR, a long-acting somatostatin analog [11,12].

IFN-α was selected in the current study for three practical reasons: IFN-α is commercially available and funded by third-party payers based on NCCN guideline recommendations; there has been no institutional clinical trial specific for this indication; and based on its mechanism of action and demonstrated activity in WHO grade 1 recurrent meningioma [7,11]. The current study used IFN-α in a subcutaneous dose schedule similar to that used to treat renal cell cancer and melanoma. IFN-α is a biological agent with modest toxicity and known activity in a variety of cancers, including meningioma [28–31]. Recombinant IFN-α has been found to inhibit the growth of cultured human meningioma cell lines *in vitro* [32]. IFN-α was, therefore, considered a reasonable alternative therapy for refractory recurrent meningioma based on the above mentioned data, in addition to evidence suggesting antiproliferative, immunomodulatory and antiangiogenic properties of IFN-α [29,32,33]. In a previous trial of recurrent WHO grade 1 meningioma refractory to surgery and RT, IFN-α demonstrated PFS at 6 and 12 months of 52 and 29%, respectively [11]. There was no evidence of an objective radiologic response to IFN-α. The best objective response rate was stable disease seen in 23 out of 31 (74%) patients. The current retrospective study of recurrent high-grade meningioma demonstrated far less single-agent activity, with a median PFS of 4 months, and a 6- and 12-month PFS of 17 and 3%, respectively, compared with the aforementioned trial of WHO grade 1 recurrent meningioma patients. However, a similar incidence of

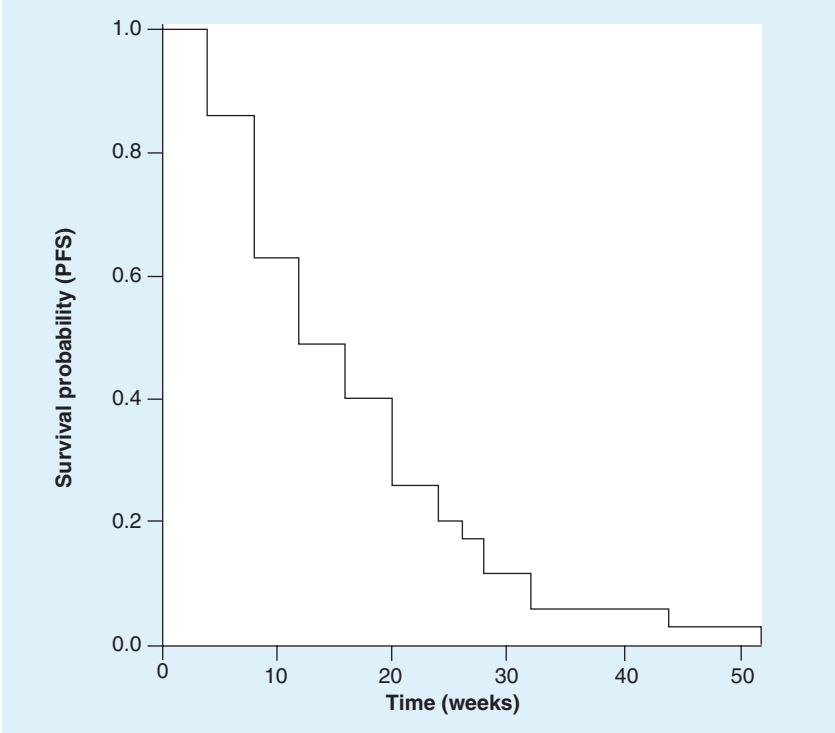

Figure 1. Progression-free survival function estimated by the Kaplan–Meier product limit method.
PFS: Progression-free survival.

Table 3. Targeted therapy for recurrent high-grade meningioma.

Inhibitor	Target	Patients (n)	Radiographic response rate (%)	Progression-free survival		Ref.
				Median (months)	6 month (%)	
Bevacizumab	VEGF	15	0	6.5	44	[17]
Bevacizumab	VEGF	14	7	NA	86	[18]
Sunitinib	VEGFR	30	0	4.6	36	[19]
Vatalanib	VEGFR	21	5.8	4.65	37.5	[20]
Imatinib	PDGFR	10	0	2.0	0	[21,22]
Imatinib	PDGFR	8	0	16	66.7	[23]
Imatinib + hydroxyurea	PDGFR	13	0	4.1	46	[24]
Erlotinib	EGFR	17	0	3.6	29	[25]
Pasireotide	sst	17	0	4.0	12	[26]
Sandostatin® LAR	sst	8	25	3.0	25	[12]
Octreotide	sst	8	0	4.0	25	[27]
IFN-α	VEGF	35	0	3.0	17	–

NA: Not available; sst : Somatostatin receptor.
Data taken from [15].

IFN-α toxicity was seen in both the previous and current study, in which anemia and fatigue were most problematic, requiring a dose reduction in approximately 20% of all patients. How to interpret the current trial is challenging, as there are very limited published data regarding recurrent high-grade meningioma treated with systemic therapies. Table 3 outlines studies carried out to date with targeted therapies for recurrent high-grade meningioma ranging from somatostatin analogs to tyrosine kinase small-molecule inhibitors and angiogenic inhibitors.

Current treatment of high-grade meningioma utilizes cytoreductive surgery with the intent of complete resection, often involving more than one surgery, as well as RT. The utilization of RT of meningioma has evolved and often utilizes both external-beam fractionated as well as stereotactic RT, most often administered at differing times during a patients' treatment history. The CNS NCCN guidelines recommend RT for partially resected WHO grade 2 meningioma, as well as for all WHO grade 3 tumors [7]. In addition, CNS NCCN guidelines commend RT (external-beam or stereotactic RT) at the time of meningioma recurrence. This treatment approach was applied in this retrospective case series as all patients underwent surgery (100% one surgery, 60% two surgeries and 6% three surgeries) and RT (100% fractionated external-beam RT and 100% stereotactic radiation) before initiating treatment with IFN-α.

A variety of targeted agents have been utilized for recurrent high-grade meningioma (Table 3), the majority with limited or no activity in recurrent meningioma. The single exception has been studies employing angiogenic inhibitors, such as targeted agents directed against the VEGF signaling pathway. The VEGF pathway has been demonstrated to be upregulated in meningioma, suggesting this pathway as a valid target for treating recurrent meningioma [34–38]. Currently, there are two anti-VEGF strategies, VEGF ligand- (bevacizumab) and VEGFR- (sunitinib and vatalanib) directed therapy, and both have been employed for recurrent meningioma [17–20]. A prospective Phase II study of bevacizumab is currently enrolling patients with recurrent meningioma of all grades, and hopefully will define the utility of this approach for recurrent high-grade meningioma. Both the sunitinib and vatalanib trial (of VEGFR inhibitors) have been scheduled for publication, but aside from abstract presentations, neither trial has been reported. As a consequence, it may be premature to draw conclusions regarding efficacy. Additionally, and importantly for VEGFR small-molecule inhibitor agents, issues of toxicity are paramount as, similar to anti-VEGF therapies, these therapies are cytostatic and will probably require long-term usage [19,20].

Defining activity for an antimeningioma systemic therapy has been problematic due to the limited literature, few prospective trials, absence of randomized trials, heterogeneity of prior treatment, wherein patients have dissimilar treatment backgrounds, and the lack of consensus regarding survival end points that permits definition of an active antimeningioma systemic therapy [21–26]. Unsurprisingly, studies have varied with respect to what constitutes a positive versus negative trial,

which is also a conundrum for the current retrospective study. In part, these differences reflect differences in prior treatments (surgery and RT), as well as differing interpretations of the limited literature regarding treatment of recurrent meningioma. What is in agreement is that all current systemic therapies are cytostatic and, consequently, objective radiographic response rate is not a useful measure of therapeutic effectiveness in recurrent meningioma. In fact, 6-month PFS appears to be the most useful and objective measure by which to compare treatments across recurrent meningioma trials. Wen *et al.* contends that an active agent for recurrent high-grade meningioma is defined by a 6-month PFS of 30% [21,22]. The Radiologic Assessment in Neuro-Oncology (RANO) working group currently has a subcommittee formulating response criteria for clinical trials in recurrent meningioma, including both low- and high-grade tumors [13].

However, significant challenges remain in the development of systemic therapies for recurrent meningioma. These include: disinterest by the pharmaceutical industry (the most common funding source for primary brain tumor clinical trials); relatively limited interest from neuro-oncology brain tumor cooperative groups, which continue to have a glioma therapeutic focus; a perception that patients with recurrent meningioma are uncommon and, therefore, a limited pool of eligible patients for clinical trials; a lack of standardized response criteria with respect to systemic therapy for recurrent meningioma; and an element of therapeutic skepticism by neuro-oncologists that systemic therapy for recurrent meningioma is of limited efficacy. These barriers to the implementation and design of clinical trials for patients with recurrent meningioma have resulted in a paucity of open trials for patients with surgery- and radiation-refractory recurrent meningioma (and those currently open are all comparatively small, single-arm Phase II studies), attesting to a continued unmet need in neuro-oncology.

In conclusion, although IFN-α is relatively nontoxic, in patients with recurrent and refractory high-grade meningiomas, IFN-α appears to have only modest activity in this comparatively large retrospective case series.

Future perspective

Over the next 5–10 years it is highly likely that new systemic therapies for recurrent meningioma will become available. The majority of these anticipated systemic therapies will evolve from further dissection of the molecular biology of meningioma, which will identify molecular targets that represent drivers of meningioma growth, survival and apoptosis. This theme of cancer therapeutics, that is, identification of cancer-specific driver mutations, has revolutionized cancer therapy; it is expected that such discoveries will also identify novel therapeutics for meningioma. The current challenge is the limited interest in systemic therapy of meningioma and corresponding clinical trials in such patients. However, there is increasing interest within the neuro-oncology community in conducting clinical trials in recurrent meningioma, which is reflected by the number of trials that have utilized angiogenic inhibitors (e.g., bevacizumab, sunitinib and PTK-787). In addition, a working group of the RANO has been charged with outlining and defining parameters of clinical trials in recurrent meningioma, which will lead to greater harmonization among trials and, hopefully, improved therapeutics.

Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Informed consent disclosure

The author states that he has obtained verbal and written informed consent from the patient/patients for the inclusion of their medical and treatment history within this case report.

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