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ORIGINAL ARTICLE

Recurrent high-grade meningioma: a phase II trial with somatostatin analogue therapy

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Abstract
Purpose A prospective, two-stage phase II trial with octreotide in patients with recurrent high-grade meningioma was conducted. The radiographic partial response (RPR) was set as the primary study endpoint, whereas progression-free survival at 6 months (PFS6) was defined as the secondary endpoint.
Methods Nine patients (eight men; median age 65) with histological high-grade meningioma (five with grade II and four with grade III) and progression after prior surgery and radiotherapy were included. All had positive brain octreotide SPECT scanning. Octreotide was administered intramuscularly once every 28 days at a dose of 30 mg for the first two cycles and 40 mg for subsequent cycles until progression. Magnetic resonance imaging was performed every 3 months. Progression and RPR were defined as an increase of ≥25 % and as a decrease of ≥50 % in two-dimensional maximum diameters, respectively.
Results Patients received a median of three octreotide cycles (range 1–8) without grade ≥2 toxicities. No RPRs were observed. Stable disease was the best response in 33.3 % ($n = 3$). All patients had progressive disease at 10 months of follow-up. Median time to progression was 4.23 months (range 1–9.4), and the PFS6 was 44.4 % ($n = 4$).
Conclusion Our study failed to provide evidence to support the use of monthly long-acting somatostatin analogue schedule in recurrent high-grade meningiomas, as none of our patients demonstrated RPR. The modest median PFS of 4–5 months along with the unknown natural history of recurrent meningiomas render the use of this therapy against these aggressive brain tumors uncertain.

Keywords High-grade meningioma · Recurrent meningioma · Meningioma · Somatostatin · Octreotide

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Introduction

Meningiomas, originating from arachnoid cap cells within the meninges, represent the most common intracranial tumor in adults. They account for 35 % of all primary brain tumors and most often occur in late adult life [1, 2]. Although the majority of meningiomas are benign and grow slowly, high-grade meningiomas are more aggressive, carrying a greater risk of recurrence and increased morbidity and mortality [3–6].

High-grade meningiomas, including atypical (WHO grade II) and anaplastic (WHO grade III), constitute 20 % of all intracranial meningiomas [2]. The current standard treatment protocols for managing these brain malignancies include maximally safe surgical resection, followed by fractioned radiation therapy of the tumor and surrounding brain parenchyma [7].

Management of meningioma recurrence after the completion of both surgery and radiotherapy is handled by re-resection, when it is surgically accessible, and

re-irradiation. Otherwise, several chemotherapy schedules and targeted therapies have been suggested as possible treatments [8]. However, existing knowledge shows that these salvage therapies have obtained a rough progression-free survival (PFS) of <25 % at 6 months, thus not achieving positive influence in the outcome and survival of patients with high-grade recurrent meningioma [9, 10]. In any case, it should be noted that clinical research on this topic is limited by the fact that the natural history of untreated meningioma remains largely unknown.

Somatostatins, also known as somatotropin release-inhibiting factors, are a family of neuropeptides produced in the hypothalamus and released into systemic circulation to act as neuromodulators as well as potent inhibitors of secretory processes and cell proliferation [11]. Somatostatin has five subtypes of receptors: sstr1–sstr5.

Meningiomas show a high frequency of somatostatin receptor expression (up to 90 %); most frequently, it is the sstr2a subtype, but their functional role in vitro remains unclear [12]. Due to their short half-life, a number of somatostatin analogues with longer half-life have been developed. Octreotide (Sandostatin; Novartis Pharmaceuticals) is a prototype of a long-acting somatostatin analogue agonist, with a clear preference for sstr2a.

Since 2007, the literature has contained small anecdotal reports of octreotide's improving meningioma-related signs and symptoms but with no radiographic improvements [13, 14]. More recently, two small-scale phase II trials showed contradictory results in terms of radiographic response [15, 16].

We report herein the results of a prospective two-stage phase 2 trial in adults with recurrent high-grade meningioma treated with octreotide who had previously undergone surgery and radiotherapy and were not candidates for re-resection or re-irradiation. The radiographic partial response (RPR) was set as the primary study endpoint, whereas the PFS6 was defined as the secondary endpoint.

Materials and methods

Eligibility criteria

Chemotherapy-naïve adult patients with a histologically confirmed diagnosis of high-grade meningioma (WHO grade II or III) and progression after prior surgery and radiotherapy were recruited from the outpatient clinic of the Institute of Oncology—Duran i Reynals during a 2-year period (September 2009–September 2011). All patients provided informed consent, and the study protocol was approved by the institutional review board.

To be eligible for enrollment, patients had to present disease recurrence after ≥2 months from the last radiation therapy and non-eligibility for safety re-resection or re-irradiation. Radiographically evaluable tumor with evidence of progression on contrast-enhanced magnetic resonance imaging (MRI) scan and the presence of somatostatin receptors in meningiomas at recurrence (positive brain octreotide SPECT scanning) were strictly required for inclusion. Additional inclusion criteria included adequate hematological, renal, hepatic and thyroid function as well as a Karnofsky performance status (KPS) ≥60 before the initiation of treatment with octreotide.

Drug schedule

The somatostatin analogue, octreotide (Sandostatin LAR), was administered intramuscularly once every 28 days at a dose of 30 mg for the first two cycles and 40 mg for subsequent cycles. The dose was reduced to the preceding level if ≥grade 2 toxicity, according to the National Cancer Institute Common Toxicity Criteria version 3.0 (NCI-CTCv3), occurred with dose escalation. Octreotide therapy was maintained until progression and was discontinued in case of evidence of >grade 2 toxicity, according to NCI-CTCv3.

Subject evaluation

Patients were clinically evaluated at baseline and before starting each octreotide cycle. Blood counts were analyzed before each cycle, and a contrast-enhanced MRI was performed every 3 months or when clinical worsening required it. As previously mentioned, the RPR was set as the primary study endpoint. The radiographic response was measured bidimensionally (two-dimensional maximum diameters) and graded as follows: (a) complete response if total disappearance of tumor was observed; (b) partial response in case of decrease in tumor size of ≥50 %; (c) progression of disease if an increase in tumor size of ≥25 % was observed and (d) stable disease in all other cases. The secondary endpoint was PFS6, defined as the time from the first day of octreotide treatment until progression. In addition, overall survival, defined as the time from the first day of octreotide treatment until death, was also examined.

Criteria for assessing efficacy

Our trial had a two-stage phase II trial design. Based on available bibliographic data, we determined that 30 % of patients enrolled in this trial were likely to obtain RPR [15]. Taking into account this estimation and using a Simon minimax two-stage study design, with an α level of 0.10 and a power of 90 %, a maximum of 21 patients (seven patients in stage 1 of the trial and 14 in stage 2) would need to be enrolled. If two or less patients responded to treatment during the first stage, the trial would have to be discontinued,

Table 1 Clinical characteristics and response of patients treated with octreotide

Patient	Age (years)	Gender	KPS	Grade	Prior therapy		Cycles of octreotide	Best response	TTP (months)	OS (months)
					Surgery	RT				
1	71	M	100	II	Simpson III	EBRT	3	PD	3.08	2.75
2	51	M	70	III	Simpson II	EBRT + SRT	3	PD	3.08	5.34
3	63	F	90	II	Simpson II	EBRT	6	SD	7.31	29.84
4	33	M	100	II	Simpson III	EBRT	8	SD	9.38	39.93[a]
5	21	M	80	II	Simpson II	EBRT	3	PD	7.48	35.28[a]
6	74	M	60	III	Simpson I	EBRT	3	PD	2.82	18.52
7	66	M	70	II	Simpson I	EBRT	4	PD	4.23	10.69
8	65	M	80	III	Simpson II	EBRT	6	SD	6.98	9.25
9	77	M	80	III	Simpson III	EBRT	1	PD	1	14.49

M male, *F* female, *KPS* Karnofsky performance scale, *RT* radiation therapy, *EBRT* external beam radiation therapy, *SRT* stereotactic radiotherapy, *PD* progression of disease, *SD* stable disease, *TTP* time to progression, *OS* overall survival

[a] Alive

whereas if three or more responses were observed at the end of the trial, we would move forward to stage 2.

Results

Nine patients (eight males and one female) with high-grade recurrent meningioma (five with grade II and four with grade III according to WHO classification) were included. They had a median age of 65 years (range 23–77) and a median KPS of 80 (range 60–100). Two patients had previously been treated with gross total resection (Simpson I) and the other seven with partial resection (four Simpson II and three Simpson III). Subsequently, all patients received radiation therapy. SPECT with octreotide was positive in all of them at relapse of the disease. The clinical characteristics of the patients are summarized in Table 1.

Patients received a median of three octreotide cycles (range 1–8 cycles) without evidence of grade ≥2 toxicities. In all patients, octreotide treatment was stopped because of disease progression. Only five patients presented gastrointestinal toxicity with diarrhea (all of them grade <2). No other treatment-related toxicities occurred, and no dose reduction was required.

As may be seen in Table 1, all nine patients were evaluable for response. No partial radiographic responses were observed. Stable disease was the best response in 33.3 % ($n = 3$). None of our patients had neurological improvement. All patients had progressive disease at 10 months of follow-up. As can be seen in Fig. 1, the median time to progression (TTP) was 4.23 months (range 1–9.38) and the overall PFS6 was 44.4 % ($n = 4$). After the progression to octreotide treatment, four patients again underwent surgery, one received a hydroxyurea-based chemotherapy schedule and the others received the appropriate supportive care due to their low performance status after the disease relapse. Overall survival was 18.7 months (range 2.7–39.9).

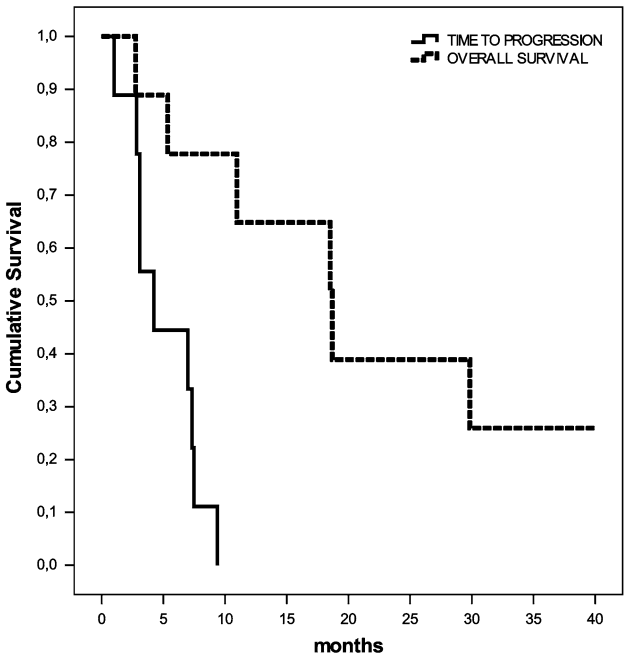

Fig. 1 Progression-free survival (*solid line*) and overall survival (*dotted line*) in patients with recurrent surgery and radiation therapy high-grade meningioma treated with octreotide

Discussion

In 2013, the Central Nervous System National Comprehensive Cancer Network (CNS NCCN version 2.2013) guidelines recommended somatostatin analogue (category 2A) and with less consensus, hydroxyurea and alpha-interferon

(category 2B) for the treatment of surgically inaccessible and radiation-refractory recurrent meningioma [7, 17].

Hydroxyurea is an antineoplastic drug that has demonstrated potent in vitro inhibition of cultured meningioma cells by inducing apoptosis [18]. Several subsequently performed retrospective studies and clinical trials in recurrent high- and low-grade meningiomas after surgery and radiotherapy demonstrated a very modest efficacy, not achieving median PFS beyond 2 months, but with acceptable levels of toxicity [9, 19–21].

Alpha-interferon is a biological agent with modest toxicity and known for its antiproliferative and antiangiogenic activity in a variety of cancers [22]. However, it has demonstrated only modest activity in a small series of meningioma patients. Recently, a phase II study with 35 patients that included only recurrent low-grade meningioma demonstrated a PFS6 of 54 % and a median PFS of 7 months without radiological responses [23].

Somatostatins play a role in several pathways relevant to cancer by inhibiting angiogenesis and invasion as well as inducing apoptosis [24]. Although in some studies, the addition of somatostatin inhibits meningioma growth, in others, it increased meningioma proliferation [25, 26]. In addition, recent data taking into account that high-grade meningiomas highly express somatostatin receptors, especially sst2A [25], have led to the launching of pilot clinical trials to inhibit high-grade meningioma aggressiveness. However, the reported results of the two largest trials conducted thus far are conflicting, particularly concerning radiographic response [15, 16].

The first prospective trial of sustained-release intramuscular somatostatin in 16 patients with recurrent low- and high-grade meningioma treated with monthly octreotide reported encouraging results. The study showed a PFS6 of 44 % with RPR in a third of patients and minimal toxicity [15]. However, a subsequent similarly designed prospective trial with daily subcutaneous octreotide in 12 patients with recurrent meningioma found a PFS6 of 33 % without evidence of radiographic response [16]. Finally, the results of another relevant trial testing the efficacy of monthly octreotide injection (Sandostatin LAR 30 mg) in eight patients with unresectable skull base meningiomas showed no tumor regression [27].

To further test the potential efficacy of salvage therapy with octreotide in patients with high-grade recurrent meningioma, we conducted the current prospective two-stage phase II trial, applying similar study design [15, 16]. Although our patients definitely presented overexpression of somatostatin receptors, as demonstrated by positive brain octreotide SPECT scanning, there was no evidence of radiographic response. Importantly, our reported PFS6 (44.4 %) was comparable to previously published data [15, 16]. Additionally, we found that therapy with octreotide was well tolerated.

In line with Johnson et al. and contrary to Chamberlain et al., our main finding was that we were unable to accomplish our primary endpoint as we failed to demonstrate any radiographic response secondary to octreotide treatment in our series of patients with high-grade meningioma. However, recent expert consensus, based on a systematic review of trials and retrospective collection series published in indexed journals, has established a response rate of PFS6 >35 % as a benchmark of probable interest in high-grade meningioma systemic therapies [28]. Unfortunately, the two-stage statistical design of our trial had established the radiographic response as main endpoint, and due to discontinuation after the first step, the final sample size obtained was too small to offer a strong conclusion regarding this point.

The homogeneity of our sample, solely comprising high-grade meningioma cases, represents the major strength of our trial and lends support to the accuracy of our findings. In contrast, one important limitation of the two previous trials was that patients with all grades of meningioma were included, thus potentially leading to bias due to heterogeneity in the population studied.

Additional strengths of our trial are the prospective design and the documentation of somatostatin overexpression in our patients prior to the initiation of therapy as an inclusion criterion. However, it should be noted that although we demonstrated selective octreotide uptake in all of our patients, we failed to subsequently demonstrate a tumor response secondary to octreotide therapy. It seems that the presence of somatostatin receptors in meningioma only reflects their expression and not their function, thoroughly supporting previous evidence suggesting that their functional role remains largely unclear [12].

To summarize, our trial failed to provide evidence to support the use of octreotide therapy against high-grade recurrent meningioma taking into account a radiographic response criterion. The lack of RPR, the modest median PFS of 4–5 months and the largely unknown natural history of recurrent meningiomas render the use of this therapy against these aggressive brain tumors uncertain. In any case, we should acknowledge that the results of this approach may be premature, and definitive conclusions await larger comparative trials. Effective treatment of high-grade recurrent meningiomas remains an unmet need in everyday neuro-oncology practice.

Conflict of interest We have no conflict of interest. No funding source had a role in the preparation of this paper or in the decision to submit it for publication.

Ethical standards The protocol was approved by the clinical research ethics committees of the center, and the trial was conducted in accordance with the guidelines of the Spanish Ministry of Health and in accordance with good clinical practice and the tenets of the Declaration of Helsinki.

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