Treatment of unresectable skull base meningiomas with somatostatin analogs

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Object. The standard surgical treatment for meningiomas is total resection, but the complete removal of skull base meningiomas can be difficult for several reasons. Thus, the management of certain meningiomas of the skull base—for example, those involving basal vessels and cranial nerves—remains a challenge. In recent reports it has been suggested that somatostatin (SST) administration can cause growth inhibition of unresectable and recurrent meningiomas. The application of SST and its analogs is not routinely integrated into standard treatment strategies for meningiomas, and clinical studies proving growth-inhibiting effects do not exist. The authors report on their experience using octreotide in patients with recurrent or unresectable meningiomas of the skull base.

Methods. Between January 1996 and December 2010, 13 patients harboring a progressive residual meningioma (as indicated by MR imaging criteria) following operative therapy were treated with a monthly injection of the SST analog octreotide (Sandostatin LAR [long-acting repeatable] 30 mg, Novartis). Eight of 13 patients had a meningioma of the skull base and were analyzed in the present study. Postoperative tumor enlargement was documented in all patients on MR images obtained before the initiation of SST therapy. All tumors were benign. No patient received radiation or chemotherapy before treatment with SST. The growth of residual tumor was monitored by MR imaging every 12 months.

Results. Three of the 8 patients had undergone surgical treatment once; 3, 2 times; and 2, 3 times. The mean time after the last meningioma operation (before starting SST treatment) and tumor enlargement as indicated by MR imaging criteria was 24 months. A total of 643 monthly cycles of Sandostatin LAR were administered. Five of the 8 patients were on SST continuously and stabilized disease was documented on MR images obtained in these patients during treatment (median 115 months, range 48–180 months). Three of the 8 patients interrupted treatment: after 60 months in 1 case because of tumor progression, after 36 months in 1 case because of side effects, and after 36 months in 1 case because the health insurance company denied cost absorption.

Conclusions. Although no case of tumor regression was detected on MR imaging, the study results indicated that SST analogs can arrest the progression of unresectable or recurrent benign meningiomas of the skull base in some patients. It remains to be determined whether a controlled prospective clinical trial would be useful.

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Key Words • meningioma • skull base • somatostatin • hormone therapy

MENINGIOMAS represent around 20% of all intracranial tumors and have a 10-year recurrence rate of 20%–50% despite aggressive surgery and irradiation.14 The standard surgical treatment for meningiomas is total resection. However, many tumors are not amenable to surgery given their deep location or proximity to delicate structures.26 The complete removal of skull base meningiomas can be especially difficult when basal vessels and cranial nerves are involved. For inaccessible tumors and those with aggressive histological or clinical features, radiation therapy is another important treatment option. Most authors recommend using standard external beam radiation therapy, whereas radiosurgical techniques may also be appropriate in selected patients.1,8 Additionally, chemotherapy is being explored as another treatment option for unresectable or growth-progressive residual meningiomas.4,35 In recent reports it has been suggested that SST administration can cause growth inhibition of unresectable and recurrent meningiomas;1,10 however, the application of SST and its analogs has not been routinely integrated into standard treatment strategies for meningiomas. Clinical studies clearly proving growth-inhibiting effects do not exist to date. We report on our experience using Sandostatin LAR in 8 patients with recurrent meningiomas of the skull base.

Methods

Between January 1996 and December 2010, 13 patients harboring progressive residual meningiomas (according to MR imaging criteria) following operative ther-
apy were treated with a monthly injection of the SST analog octreotide (Sandostatin LAR 30 mg, Novartis). Eight of the 13 patients had a meningioma of the skull base and were analyzed for this study. Postoperative tumor enlargement was documented in all patients on MR images obtained before the initiation of SST therapy. The term “growth progressive” in this study is used for tumors that have shown progression of growth according to MR imaging criteria. The PFI before SST treatment was defined as the time range from the last surgery to tumor enlargement visible on MR imaging and was not defined clinically; PFI during SST treatment was defined as the time from the onset of SST treatment to tumor progression according to MR imaging. All patients had actively growing residual tumors according to MR imaging at the onset of SST therapy. Informed consent was obtained from all treated patients before the application of SST. To decide which patients were suitable for treatment SST scintigraphy using 111I-labelled DTPA-octreotide (according to Hildebrandt et al.) was performed in all patients, showing a high uptake. Tumor growth during SST therapy was monitored by serial MR imaging every 12 months. The PFI after the onset of SST therapy was defined as the time range from the first SST injection to tumor enlargement according to MR imaging and not clinical changes.

**Results**

A summary of the cases is featured in Table 1. The mean age of our cohort at the beginning of SST therapy was 50.5 years (median 52 years). Seven of the 8 patients were women. Three patients underwent surgery 1 time; 3 patients, 2 times; and 2 patients, 3 times (mean number of surgeries 1.875). The mean time from the initial diagnosis to the onset of SST therapy was 5.5 years (median 3 years, range 0.5–21 years). The most common tumor location was the sphenoid wing (5 of 8 patients). Histological verification of a meningioma by resection or biopsy was performed in all patients. All tumors were benign (WHO Grade I), and no patient received radiation or chemotherapy either before or during SST treatment. The mean time from the last meningioma operation to tumor enlargement on MR imaging was 24 months. Six hundred forty-three monthly cycles of SST were administered. Two of 8 patients interrupted treatment without signs of tumor progression, after 36 months in 1 case because of side effects and after 36 months in 1 case because the health insurance company denied cost absorption. Six of 8 patients were continuously on SST. Five of these 6 patients had stabilized disease documented on MR images obtained during treatment to date (median 115 months, mean 102 months, range 48–180 months). One of 6 patients showed tumor growth on MR imaging after 60 months of therapy. No case of tumor regression was detected on MR imaging, and no case showed clinical improvement during SST treatment. Sandostatin LAR was reasonably well tolerated, except in 1 patient who experienced psychiatric side effects.

**Discussion**

It is important that more effective medical therapy is developed for growth-progressive residual or recurrent meningiomas. There is a subgroup of patients that has persistent recurrences despite multiple resections and/or progress through radiotherapy. The use of chemotherapy might obviate the need for further surgical procedures in certain patients and offer another treatment option in patients with tumor progression through surgery and irradiation. Although early attempts at chemotherapy with traditional antineoplastic agents and hormonal approaches have been disappointing, treatment with hydroxyurea may prove to be efficacious.

In the current study, we used an alternative method of hormone therapy by using the SST analog octreotide (Sandostatin LAR). Somatostatin is a natural peptide hormone secreted in various parts of the human body. The biological effects of SST are mediated through its specific receptors (SSTRs 1–5). Endogenous SST’s short half-life in circulation (1–3 minutes) makes it difficult to use continuously and has resulted in the development of synthetic analogs. The cyclic octapeptide octreotide is more resistant to peptidases, and its half-life and hence its biological activity is substantially longer than for native SST (1.5–2 hours vs 1–2 minutes). The development of a depot formulation of octreotide, Sandostatin LAR, which was

<table>
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<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>Lesion Location</th>
<th>No. of Ops Since Initial Dx</th>
<th>Time From Dx to Last Op (yrs)</th>
<th>PFI After Last Op (mos)</th>
<th>PFI on SST (mos)</th>
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<td>2</td>
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<td>60</td>
<td>progression after 60 mos</td>
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* spw = sphenoid wing.
† Interruption of SST therapy without tumor enlargement.
administered up to 30–60 mg once every 4 weeks, has to a large extent eliminated the need for daily injections. There are 5 different G-protein–coupled SSTR subtypes (SSTRs 1–5), and the majority of meningioma cells show positivity for at least 1 of the 5 SSTR subtypes. One cell proliferation study evaluating a possible role of blocked SSTR in the control of human meningioma cell growth showed a significant inhibition of DNA synthesis in 4 of 5 tissue cultures, and the authors suggested promising effects against meningiomas. In contrast, another analysis showed no direct growth-inhibiting action on cultured human meningioma cells. Rather, there was a slight but significant stimulation of growth in the presence of SST. The authors concluded that therapeutic trials in patients with recurrent or inoperable meningiomas with somatostatin analogs must be performed with caution. The first case reports concerning the obvious effect of SST on meningioma have been published since 1989. One report showed rapid clinical improvement in patients on octreotide, although no radiological signs of tumor regression were detected. In contrast, De Menis et al. documented the growth of a meningioma during treatment with octreotide for acromegaly. Octreotide effectively suppressed growth hormone secretion but could have stimulated the growth of the tentorium meningioma since SST did not significantly influence the in vitro proliferation of the patient’s cultured tumor cells. The results of our study are similar to those of Chamberlain and colleagues, who also used Sandostatin LAR in 16 patients with recurrent intracranial meningiomas. Ten of the 16 patients responded to or stabilized on SST (median 27 weeks, range 5–39 weeks), while disease in the other 6 patients progressed. Five of our 6 patients remained stable on SST (median 115 months, range 48–180 months), and disease progressed in only 1 patient after 60 months of treatment. The overall PFS was 44% (7 of 16 patients) at 6 months in the Chamberlain and colleagues series. The PFS in our study was 100% at 48 months and 83.3% (5 of 6 patients) at a median of 87.5 months, resulting in a median PFI of 87.5 months during SST treatment (compared with a median PFI of 30 months in these patients before SST therapy). The more extended follow-up of responsive patients in our study, as compared with that in the study of Chamberlain et al. (median 115 vs 5 months), verifies that stabilization of disease with SST in responsive patients can be quite durable. In contrast to the collective sample of Chamberlain et al., none of our patients had radio- or chemotherapy after surgery (denied by either the radiooncologists or the patients themselves). In their study, 14 of 16 patients underwent surgery, 13 of 16 had radiation therapy, and 12 of 16 had chemotherapy before beginning SST therapy. They treated 8 of 16 patients with malignant meningiomas, whereas we treated exclusively benign tumors. Chamberlain and colleagues’ patients received 2–15 cycles of SST (total 92 cycles, median 4.5 cycles) with minimal toxicity. In our patients, 36–180 cycles (total 643 cycles, median 54 cycles) were administered, and we documented 1 patient with newly diagnosed depression during SST treatment. This patient wished to interrupt the treatment after 36 cycles, although this side effect is not described as a typical one and no tumor progression was detected.

Our results suggest that Sandostatin LAR might have modest activity in patients with unresectable or progressive meningiomas of the skull base. The strength of our data is weakened because of the low number of treated patients. In addition, the natural history of meningiomas is such that unpredictable intervals of slow growth or no growth can occur in some patients. Zeidman et al. found 2 of 21 patients without tumor growth during a mean postoperative interval of 3.64 years (range 2.08–10.83 years). One study examining 33 patients with meningiomas showed a median relative growth rate of 14.18% per year, and the median tumor doubling time was 5.228 years. Another study of 41 patients with meningiomas treated conservatively showed a comparable mean annual growth rate (14.6%, range 0.48%–72.8%), and the mean tumor doubling time was 21.6 years. The median postoperative time to tumor enlargement on MR imaging among 38 patients with subtotal resected residual petroclival meningiomas was 66 months (87.5 months in our report), and the 5-year PFS rate (indicated by MR imaging criteria) was 60% (75% in our study).

Therapeutic costs for Sandostatin LAR are around US $2000/month for each injection. Compared with stereotactic radiosurgery (around US $6500 for a single-fraction treatment or US $3500 + US $1000 for every 2 additional fractions in hypofractionated therapy), the SST therapy is more costly after 4–6 months of treatment (according to the table of charges for physicians in Germany). Note, however, that radiotherapy after postoperative tumor enlargement on MR imaging was not performed in our 8 patients with skull base meningiomas (denied in 2 cases by the radiooncologists and in 6 cases by the patients themselves).

Somatostatin analogs like octreotide (Sandostatin LAR) are traditionally used to treat acromegaly and neuroendocrine tumors of the gastrointestinal tract. About 88% of the meningiomas analyzed (37 of 42 lesions) were positive for at least 1 of the 5 SSTR subtypes, displaying a variable pattern of mRNA expression of the different SSTR subtypes. Messenger RNA from SSTRs 1 and 2 was the most frequently detected, and in half of the meningioma cells 3 or more SSTRs were detected. Especially the binding of SST on SSTR2 decreases the production of vascular endothelial growth factor with a reduction in peritumoral edema and is perhaps one factor inhibiting meningioma growth. The different receptor subtype binding affinities seem to result in different biological and clinical activities. The effects of the SST analogs are mainly mediated by interaction with SSTRs 2 and 5, while the new SST analog pasireotide (SOM230) shows higher binding capacity toward SSTRs 1, 2, 3, and 5 with no agonist activity at SSTR4. As a consequence, this substance might have a higher growth-inhibiting potential on meningioma cells than Sandostatin LAR.

Conclusions

Data suggest that SST analogs might have modest activity against recurrent and inoperable skull base meningiomas and could induce long-term stabilization of tumor growth in some patients. Although no case of tumor regression was detected in our study, the results indicate...
that Sandostatin LAR may arrest the progression of unresectable or recurrent benign meningiomas of the skull base. Further clinical trials (prospective and randomized) with larger patient cohorts and longer follow-up periods will be necessary to confirm the activity of SST analogs against meningiomas.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Schulz. Acquisition of data: Mathieu. Analysis and interpretation of data: Schulz. Critically revising the article: Mauer. Reviewed final version of the manuscript and approved it for submission: Mauer. Study supervision: Kunz.

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