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Octreotide Long-Acting Release and Everolimus for Recurrent Meningiomas

Rapid Review

CADTH

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Abbreviations

AE	adverse events
CI	confidence interval
CNS	central nervous system
LAR	long-acting release
OE	octreotide long-acting release in combination with everolimus
OS	overall survival
PFS	progression-free survival
RCT	randomized controlled trial
RT	radiotherapy
ST	systemic therapy or treatment

Key Messages

- The systematic search resulted in 1 single-arm prospective study and 1 retrospective cohort study. No relevant randomized controlled trials, systematic reviews, or evidence-based guidelines were identified that met the criteria for this review.
- Evidence was limited, inconsistent, and of low quality for the clinical effectiveness of octreotide long-acting release in combination with everolimus in patients with recurrent meningiomas.
- The quantity and quality of current publications were not sufficient to draw a conclusion in support of or against the clinical effectiveness of octreotide long-acting release in combination with everolimus relative to other systematic therapies in patients with recurrent meningiomas.
- Additional research is required to inform decision-making in this context.

Context and Policy Issues

According to the Brain Tumours Registry of Canada (2019),[1] between 2013 and 2017 of tumours of the meninges, meningioma was the most common tumour, consisting of 23.8% of all central nervous system (CNS) tumours and 37.5% of all non-malignant CNS tumours. In addition, females had higher rates of tumours of the meninges than males. With an estimated incidence of 2.3 to 8.3 in 100.000 individuals, meningiomas are the most common primary brain tumours in the US.[2]

A WHO classification for CNS brain tumours grades meningioma based on clinical outcomes as WHO I, WHO II, and WHO III, representing benign, atypical, and anaplastic meningiomas, respectively.[3] Although most meningiomas are benign (70% to 80%) and slow-growing, atypical and anaplastic meningiomas are more aggressive with a tendency for recurrence, worse clinical outcomes, and higher disease-specific mortality.[3] The rate of recurrence and the risk of transformation to malignancy is dependent on the histopathological type of meningioma. Prompt diagnosis and understanding of the severity of the tumour play a prominent role in the management of the disease.[4] Current evidence suggests individualizing indications for treatment and with consideration for factors such as age, comorbidity, life expectancy, patient preference, histologic grade, molecular factors, tumour location, and extent of resection.[5]

Surgical resection and/or radiotherapy (RT) are common therapeutic interventions for patients with meningioma.[6] However, complete surgical resection might not be possible in patients with the tumour located in an anatomically challenging position. For such patients, RT might be used alone or following subtotal surgical resection. In addition, few studies report the benefits of these interventions, and the tumours may recur in many patients depending on surgical resection, RT series, and other effective variables.[6] Although subsequent surgical resections may be suggested for patients with a recurrence, they might not be a viable option for some patients, such as those with skull base tumours. Where further surgical resections or RT are not recommended, systemic therapy (ST) may be considered. To date, a variety of STs has been used for treating recurrent meningioma (e.g., chemotherapy, hormonal therapy, targeted therapies, and biologic drugs), but the response rate and the efficacy of systemic drugs have not been yet promising.[5]

Therapeutic alternatives are limited for aggressive and recurrent meningiomas.[7] According to an in vitro study, the combination of octreotide long-acting release (LAR) and everolimus may have an additive antiproliferative effect on recurrent meningiomas.[8] Generics octreotide LAR and everolimus are available in Canada. However, a Health Canada Notice of Compliance does not exist for either octreotide[9] or everolimus[10] in patients with recurrent meningiomas, and CADTH's reimbursement review process does not typically review generic drugs. In August 2022, CADTH published a reference list on this topic that identified some relevant studies.[11] The objective for this report was to systematically summarize and critically appraise the evidence regarding the clinical effectiveness of octreotide LAR, a somatostatin agonist, in combination with everolimus, a mechanistic target of rapamycin (mTOR) inhibitor, in patients with recurrent meningioma.

Research Question

What is the clinical effectiveness of octreotide long-acting release in combination with everolimus in patients with recurrent meningiomas?

Methods

Literature Search Methods

This report is based on a literature search developed for a previous CADTH report.[11] For the previous report, a limited literature search was conducted by an information specialist on key resources including MEDLINE, Embase, the Cochrane Database of Systematic Reviews, the International HTA Database, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy consisted of both controlled vocabularies, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were meningiomas, octreotide, and everolimus. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was completed on August 17, 2022; and was limited to English-language documents published since January 1, 2017.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, were duplicate publications, or were published before January 1, 2017.

Critical Appraisal of Individual Studies

The included publications met the selection criteria and were critically appraised by 1 reviewer using the Downs and Black checklist[12] for randomized and non-randomized studies. Summary scores were not calculated for the studies; rather, the strengths and limitations of each publication were described narratively as detailed in Appendix 3.

Summary of Evidence

Quantity of Research Available

A total of 55 citations was identified in the literature search. Following the screening of titles and abstracts, 53 citations were excluded and 2 potentially relevant reports from the electronic search were retrieved for full-text review. One potentially relevant publication was retrieved from the grey literature search for full-text reviews. Of these potentially relevant articles, 1 review publication was excluded, and 2 non-randomized studies that met the inclusion criteria were included in this report. Appendix 1 presents the PRISMA[13] flow chart of the study selection.

Additional references of potential interest that did not meet the inclusion criteria are provided in Appendix 5.

Summary of Study Characteristics

Additional details regarding the characteristics of included publications are provided in Appendix 2.

Study Design

One of the 2 included non-randomized studies (authored by Graillon and colleagues) was a single-arm prospective phase II study on octreotide LAR in combination with everolimus (OE) published in 2020.[7]

The second study was a retrospective cohort study by Cardona and colleagues[14] comparing the effectiveness of OE versus sunitinib for recurrent aggressive meningiomas in patients with recurrent or refractory meningiomas at 2 reference centres. It was published in 2019.

Table 1: Selection Criteria

Criteria	Description
Population	Patients diagnosed with recurrent meningiomas
Intervention	Octreotide long-acting release in combination with everolimus
Comparator	Other therapies (i.e., hydroxyurea, bevacizumab, sunitinib, imatinib), octreotide alone, everolimus alone, no comparator
Outcomes	Clinical effectiveness, including benefits (i.e., progression-free survival, overall survival, response rate, duration of response, quality of life), and harms (i.e., safety [e.g., adverse events of ≥ grade 3 and grade 4], mortality)
Study designs	Health technology assessments, systematic reviews, randomized controlled trials, non-randomized studies

Country of Origin

The single-arm prospective study was conducted in France[7], and the retrospective cohort study was performed in Colombia.[14]

Patient Population

The prospective phase II study by Graillon and colleagues included 20 patients: 11 (55%) females and 9 (45%) males, with a mean age of 55 years (range 30 to 75). Patients had a Karnofsky performance status of at least 50% and histologically confirmed meningioma of grade 1 (n = 2, 10%), grade 2 (n = 10, 50%), or grade 3 (n = 8, 40%), who were ineligible for further surgery and/or RT. The Karnofky performance test is a standard scale ranging from 0 (death) to 100 (no evidence of disease, no symptoms) for measuring the ability of patients with cancer to perform ordinary tasks.[15] In addition, a documented progression based on 2 different MRIs confirming an increase in 2-dimensional tumour area of at least 5% per 3 months or at least 10% for 6 months before inclusion was required. The history of ST was acceptable. A life expectancy of greater than 3 months and adequate hematologic, renal and hepatic functions were also required. What adequate amount means for these measures was not reported in the article. Four patients had neurofibromatosis type 2 (NF2) germline mutation. The location of tumours was convexity, parasagittal (21, 60%); skull base (9, 26%); and intraventricular (4, 11%).

The retrospective cohort study (2019)[14] was based on a review of records of 31 patients, including 22 (71%) females and 9 males (29%), with a mean age of 55 years (range 22 to 88). The included patients had WHO II or WHO III recurrent or refractory meningiomas and had received ST if they had 1 to 5 previous relapses. The most prevalent histology was anaplastic meningioma, which was reported in 20 (65%) patients. A total of 8 (26%) patients had multicentric diseases. Bone involvement was present in nearly half of the patients, and brain invasion was reported in 13 (41.2%) patients with grade III tumours. The location of tumours was anterior fossa (13, 42%), parasagittal (8, 26%), middle fossa (5, 16%), convexity (4, 13%), and posterior fossa (1, 3%).

Interventions and Comparators

In the prospective study,[7] everolimus was orally administrated at a fixed dosage of 10 mg per day. Doses could be decreased by 5 mg in case of adverse events (AE). In addition, 30 mg octreotide was administered monthly by an intramuscular injection until tumour progression. The study duration was 1 year, which was extended to 3 years in case of disease stabilization.

In the retrospective cohort study,[14] patients were treated with OE (30 mg intramuscular octreotide every 28 days in combination with10 mg oral everolimus per day), oral sunitinib (50 mg per day for days 1 to 28 of 42 days), or bevacizumab (10 mg/kg IV on days 1 and 15). The median time elapsed between RT and the beginning of the first line of ST was 22.9 months (95% CI, 1.8 to 189.0).

The retrospective cohort study was unclear about the intervention groups and the number of patients in the study groups. Notably, the information provided in the abstract and methods and/or results was not consistent. Two study groups were identifiable based on treatment sequences (representing 1st, 2nd, and 3rd lines). The groups were OE, sunitinib, and bevacizumab; and sunitinib, OE, and bevacizumab in the abstract, but everolimus, sunitinib, and bevacizumab; and sunitinib, everolimus, and bevacizumab in the methods and results section of the paper. In addition, according to the abstract, a total of 14 patients received OE, 11 received sunitinib, and the remaining 6 received other second-line drugs (N = 31). However,

based on the results, 19 patients received everolimus or OE, and 11 patients received sunitinib (N = 30).

Outcomes

In the prospective study,[7] patients were clinically evaluated monthly. Cerebral MRI was performed at inclusion and then every 3 months until progression for all patients. The determination of progression was assessed using the Response Assessment in Neuro-Oncology (RANO) criteria.[16] Based on the RANO criteria in the intention-to-treat (ITT) population analysis, the 6-month progression-free survival rate (PFS6) was the primary end point of this study. The PFS6 is estimated to be 11% to 15% in untreated recurrent meningiomas, and treatment is considered of interest if PFS6 exceeds 35%.[17] The study hypothesized that OE could improve this rate by up to 40%. A per-protocol (PP) population was defined as the population that fulfilled the inclusion and exclusion criteria and underwent at least 2 months of treatment. The maximum tumour diameter, 2-dimensional tumour area, and 3D volume were assessed. Patients with a treatment duration of less than 2 months, missing data, non-measurable initial volume, or very high tumour growth rate (> 300%/3 months) were excluded from the growth rate substudy. Safety was evaluated based on the National Cancer Institute's Common Terminology Criteria for Adverse Event version 4.0. In summary, PFS6, overall survival (OS), response rate, tumour growth rate, and safety were the outcomes reported.

In the retrospective cohort study,[14] patients were evaluated by physical examination every 3 weeks and MRI scans every 8 weeks. Assessment of response was based on RANO criteria.[16] Routine laboratory studies were assessed each month or earlier if medically indicated. Toxicities were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0. Every therapy was discontinued after disease progression or toxicity. Overall, PFS rate, OS rate, response rate, and safety (i.e., toxicities) were reported as outcomes.

Summary of Critical Appraisal

The prospective study[7] provided adequate information on the main objective, outcomes assessed, patient characteristics, and interventions received. The main findings were analyzed and described using the Kaplan–Meier method with a 95% confidence interval (CI), and the results were presented with actual probabilities. The incidence of AEs also was reported in detail. The study setup consisted of accurate (valid and reliable) outcome measures, and evidence of the risk of false positives was not observed. Moreover, the description of the staff, places, and facilities associated with treatment were representative of the treatment administered. However, the study didn't report the estimates of random variability (e.g., range or standard deviation [SD]) in the data for the main outcomes. The generalizability of the outcomes and the ability for assessing comparative effectiveness were unknown given that the outcomes were derived from a single-arm prospective study in a cohort that might not be representative of the eligible population. The impact of potential confounding factors (e.g., health history, other diseases, drug history, drug interactions, age at onset of illness, socioeconomic status, and the extent of support network) on the outcomes was not described. In addition, the investigators did not perform a sample size calculation and it was unknown if the study was adequately powered to identify statistically significant differences for all outcomes.

In the retrospective cohort study,[14] the objective and patient characteristics were properly described. The main findings were assessed using the Kaplan–Meier method and the

Log-Rank test with 95% CI, and the results were presented along with actual probabilities. The staff, places, and facilities associated with treatment were representative of the procedures received by patients. However, the information provided in the abstract and the body of the article was inconsistent, and the study reporting was unclear about treatment sequences (i.e., study groups) and the number of patients in the study groups. The estimates of random variability (e.g., range or SD) in the data for the main outcomes were not reported. The outcomes were likely to be effected by confounding factors due to selection bias because of limitations in recruiting patients into the different intervention groups. For example, the treatment selection was based on some factors such as AE profile, patient preferences, and the availability of insurers). Other examples of confounding factors not considered in this study were: crossover after progression or intolerability of the first line of medication, a low and variable number of patients in the sequences and/or lines of treatment, the variable time on medication, and the previous exposure to a medication. Toxicities were reported as the only AEs and other potential AEs were not described. Moreover, the investigators did not report a sample size calculation and it was unknown if the study was adequately powered to identify statistically significant differences for all outcomes. Overall, the outcomes of the study may not have enough generalizability to the population of interest.

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

Summary of Findings

Appendix 4 presents the main findings of the 2 included studies.[7,14]

The findings are presented by main outcomes consisting of PFS rate (Table 4), OS rate (Table 5), tumour growth rate (Table 6), response rate (Table 7), and treatment safety (Table 8).

Clinical Effectiveness of Octreotide LAR in Combination With Everolimus in Recurrent Meningioma

PFS Rate

In the prospective study,[7] in the ITT population analysis, the PFS6 rate was 55% (95% CI, 31.3 to 73.5) with a median of 6.6 months (95% CI, 2.7 to 15.0), and the 12-month PFS rate (PFS12) was 30% (95% CI, 12.2 to 50.1). In PP analysis, the PFS6 and PSF12 rates were 61.1% (95% CI, 35.3 to 79.2) and 33.3% (95% CI, 13.6 to 54.5), respectively.

In the retrospective cohort study,[14] no statistically significant difference was found in PFS between the treatment with OE (median = 12.1 months; 95% CI, 9.2 to 21.1) and sunitinib (median = 9.1 months; 95% CI, 6.8 to 6.8) (P = 0.43).

OS Rate

In the prospective study,[7] 6-month and 12-month OS rates in ITT analysis were 90% (95% CI, 65.6 to 97.4) and 75% (95% CI, 50.0 to 88.7), respectively.

In the retrospective cohort study,[14] the median OS for the cohort after initiating medical treatment was 37.3 months (95% CI, 28.5 to 42.1). The OS of the group treated with the OE, sunitinib, and bevacizumab sequence was 6.5 months longer than the OS of the group treated with the sunitinib, OE, and bevacizumab sequence. The difference was statistically significant (36.0 versus 29.5, P = 0.0001). Other variables, such as the extension of the initial surgery, the

time between diagnosis and the start of medical treatment (higher or lower than 20 months), the number of recurrences, age, and sex had no statistically significant impact on the OS rate.

Tumour Growth Rate

In the prospective study,[7] the median preinclusion surface growth rate per 3 months was 42% (range: 10% to 269%), during a median follow-up of 21 months. The volume growth rate was compared before inclusion and during treatment by independent MRI reviews. Patients with tumour progression at 3 months were considered for the 6-month analysis. A statistically significant decrease (> 50%, P = 0.0002) in the volume growth rate was observed in 78% of patients (21 out of 27 tumours) at 3 months, with a reduction in mean and median growth rates from 43.5% and 16.6% before treatment to 4.2% and 0.0% after treatment, respectively. In addition, at 6 months, a statistically significant decrease (P = 0.0003) in the volume growth rate was found in 67% of patients (12 out of 18 tumours) with reduced mean and median growth rate from 49.0% and 19.2% before treatment to 5.0% and 0.48% after treatment, respectively. In addition, long-term (i.e., > 2 years) tumour growth control was reported in 3 patients.

Response Rate

In the prospective study,[7] no complete or partial response was observed in compliance with the RANO criteria, except for the disappearance of 2 separate subcutaneous nodules in 1 patient.

In the retrospective cohort study,[14] stable disease and partial responses were reported for 6 (43%) and 4 (28.6%) of OE patients, respectively; and 7 (63.6%) and 4 (36.4%) of sunitinib patients, respectively.

Treatment Safety

In the prospective study,[7] stomatitis (i.e., swelling and redness of the mouth lining) was reported in 11 (55%) patients, including 3 with grade III AEs requiring discontinuation of both drugs in 1 patient and discontinuation of everolimus alone in another patient. Other AEs were asthenia and fatigue 9 (45%), hypercholesterolemia 9 (45%), abdominal pain and diarrhea 8 (40%), cutaneous rash 6 (30%), hypertriglyceridemia 6 (30%), hyperglycemia and diabetes 5 (25%), aspartate aminotransferase/alanine aminotransferase (ASAT/ALAT) increase 4 (20%), nausea and vomiting 3 (15%), neutropenia 2 (15%), pneumopathy 1 (5%), and cholelithiasis 1 (5%).

In the retrospective cohort study,[14] all patients in the 2 treatment sequences experienced a level of toxicity. Irrespective of the line of treatment, the most common side effects were grade 1 or 2 fatigue (12 [86%]) and grade 1 or 2 edema (2 [14%]) for OE, and grade 1 or 2 fatigue (7 [73%]) and hypothyroidism (2 [18%]) for those exposed to sunitinib. Moreover, treatment with sunitinib led to grade 3 fatigue and a dose reduction in 3 (9.7%) patients; and exposure to bevacizumab was associated with deep vein thrombosis in 2 (6.4%) patients.

Limitations

Only 2 observational, non-randomized trials (i.e., a prospective single-arm study[7] and a retrospective cohort review of records[14]) were identified on the clinical effectiveness of OE in patients with recurrent meningiomas. In the single-arm trial,[7] 20 patients received the

intervention of interest and were followed for 6 and 12 months. Because of the absence of a control treatment (i.e., no comparator), single-arm studies are not appropriate for demonstrating the comparative benefit of an intervention.[18] In the retrospective cohort study,[14] the effectiveness of OE versus sunitinib was assessed by reviewing the records of 31 patients non-randomly divided into treatment groups, which might not be representative of the eligible population. The study was unclear over the sequences and lines of treatment as well as the number of patients in study groups. Both studies were unclear regarding how the sample size was calculated and had heterogeneity in patients in terms of tumour grade and location and the history of surgery, RT, radiosurgery, and/or chemotherapy might have affected the outcomes. These limitations are concerns for accurately interpreting the results and may have an impact on the generalizability of the findings.

Overall, an insufficient number of studies and a lack of high-quality evidence, especially RCTs, create uncertainties about the validity and generalizability of the treatment outcomes with OE in patients with refractory or recurrent meningiomas. In addition, the 2 studies were conducted in France and Colombia. It is unclear how generalizable these findings may be to the Canadian context.

Conclusions and Implications for Decision- or Policy-Making

This report summarizes the available evidence on the clinical effectiveness of OE for patients diagnosed with recurrent meningiomas from 1 single-arm prospective study[7] and 1 retrospective cohort review of patients' medical records.[14] Whereas, the findings of the single-arm study were in support of improved PFS and OS rates and a reduced tumour growth rate, and results from the retrospective cohort study[14] suggested that OE and sunitinib had similar efficacy and safety profiles. In addition, a range of AEs such as stomatitis, asthenia, abdominal pain, hypercholesterolemia, cutaneous rash,[7] fatigue, and edema[14] in exposure to OE, and fatigue and hypothyroidism in exposure to sunitinib[14] were reported.

Besides being non-randomized, both included studies were relatively small (i.e., with 31 patients or less) and patients were unlikely to be representative of the patient population for whom the interventions may be indicated. Therefore, there are concerns about the risk of selection bias, low generalizability of the findings, and uncertainty of the power of the studies to determine statistically significant differences in treatment effect between the interventions.

Overall, the evidence identified for the clinical effectiveness of OE is considered to be of low quality and associated with high heterogeneity, inconsistency, imprecision, and risk of bias.[7,14] Because of the limited number of relevant studies and the low quality of existing evidence, it is hard to draw a conclusion regarding the clinical effectiveness of OE for patients with recurrent meningiomas.

Additional research with rigorous methodological approaches, such as well-designed and sufficiently powered RCTs, is needed to reduce uncertainty, inconsistency, and the risk of bias in the current available evidence, improve the generalizability of findings, and support stakeholders with decision-making regarding the use of OE in patients with recurrent meningiomas in the Canadian context.

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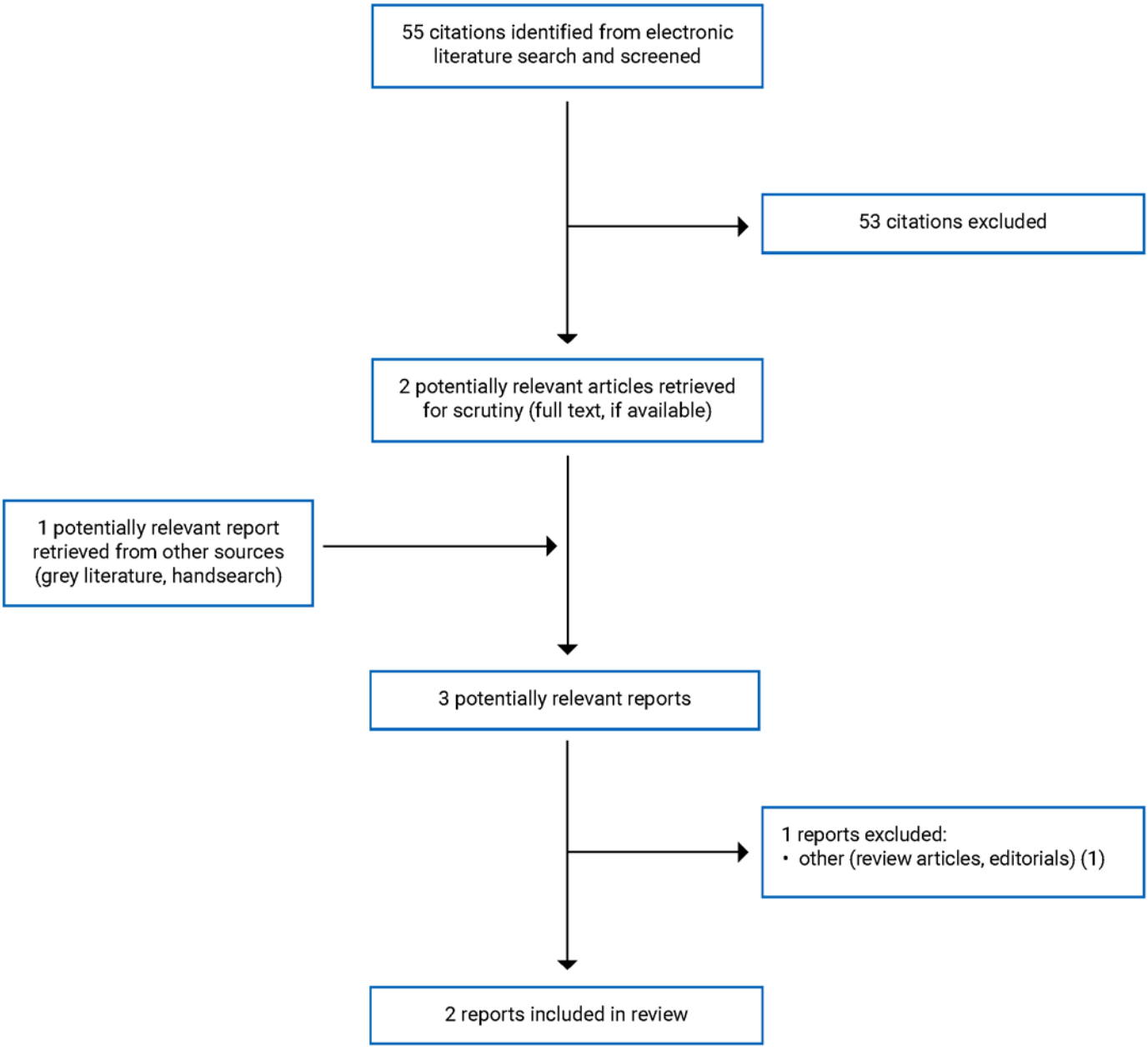
Appendix 1: Selection of Included Studies

Figure 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Note that this appendix has not been copy-edited.

Table 2: Characteristics of Included Primary Clinical Studies

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Graillon et al. (2020)[7] France **Funding:** French National Cancer Institute funding (PHRCK 2013)	A prospective, single-arm study	**N** = 20 **Age** = 55 years (30 to 75) **Female n** = 11 (55%) **Number of growing tumours** NF2 patients = 20 Non-NF2 patients = 15 **Tumour grade, n (% patients)** Grade I = 2 (10) Grade II = 10 (50) Grade III = 8 (40) **Tumour location, n (% tumours)** Convexity, parasagittal = 21 (60) Skull base = 9 (26) Intraventricular = 4 (11) **Previous surgery, n (%)** One = 2 (10) Multiple = 18 (90) **Previous radiotherapy or radiosurgery, n (%)** None 1 (5) One 10 (50) Multiple 9 (45) **Previous chemotherapy, n (%)** Yes = 5 (25) No = 15 (75)	**Intervention:** Everolimus was orally administrated at a fixed dosage of 10 mg/day. Doses could be decreased by 5 mg in case of an adverse event. 30 mg octreotide long-acting release was administrated monthly by an intramuscular injection until tumour progression. The study duration was 1 year. It was extended to 3 years in case of disease stabilization. **Comparator**: NA	**Outcomes:** a. Six-month PFS b. OS c. Tumour growth rate d. Response rate e. Safety (i.e., AEs) **Follow-up:** Median = 21 months
Cardona et al. (2019)[14] Colombia **Funding:** Andre's F. Cardona	A retrospective cohort study	**N** = 31 **Age** = 55 years (28 to 88) **Female n** = 22 (71%) **Tumour grade, n (% patients, 95% CI)** Grade II = 11 (35, 19 to 52) Grade III = 20 (65, 48 to 81) **Tumour location, n (% tumours, 95%**	**Intervention:** Treatment with: OE (as 30 mg octreotide intramuscular injection every 28 days plus 10 mg oral everolimus per day), Su (50 mg taken by mouth per day for days 1 to 28 of 42 days), or Bev	**Outcomes:** a. PFS b. OS c. Response rate d. Safety (i.e., AEs) **Follow-up:** Median = 31.8 months

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		CI) Anterior fossa = 13 (42, 25 to 59) Parasagittal = 8 (25, 10 to 41) Middle fossa = 5(16, 3 to 29) Convexity = 4 (13, 11 to 25) Posterior fossa = 1 (3, 0 to 9) **Previous recurrence, n (%, 95% CI)** 1 = 4 (13, 11 to 25) 2 = 9 (29, 13 to 45) 3 = 10 (32, 16 to 49) 4 = 5 (16, 3 to 29) 5 = 3 (10, 0 to 20) **Previous surgery, n (%, 95% CI)** 1 = 2 (6, 0 to 15) 2 = 19 (61, 44 to 78) 3 = 6 (19, 5 to 33) 4 = 1 (3, 0 to 9) 5 = 3 (10, 0 to 20) **Multicentricity** = 8 (26) **The extent of resection, n (%, 95% CI)** Total = 14 (45, 27 to 62) Subtotal = 17 (55, 37 to 72)	(10 mg/kg IV, days 1 and 15). Treatment had 2 different sequences: • OE, Su, and Bev • Su, OE, and Bev Every therapy was discontinued after disease progression or toxicity. **Comparator**: Su	

AEs = adverse events; Bev = bevacizumab; CI = confidence interval; NA = not applicable; NF2 = neurofibromatosis type 2; OE = octreotide long-acting release in combination with everolimus; OS = overall survival; PFS = progression-free survival rate; Su = sunitinib.

Appendix 3: Critical Appraisal of Included Publications

Note that this appendix has not been copy-edited.

Table 3: Strengths and Limitations of Clinical Studies Using the Downs and Black Checklist[12]

Strengths	Limitations
Grallon et al. (2020)[7]	
The objective, main outcomes assessed, patient characteristics, and interventions received were clearly described in the introduction and/or methods sections. The source of funding was clearly stated. The study used accurate (valid and reliable) outcome measures. The main findings were clearly analyzed and described using the Kaplan–Meier method with 95% CI. The results included actual probabilities. AEs were reported in detail. Evidence of data dredging or the risk of false positives was not observed. The staff, places, and facilities associated with treatment were representative of the treatment procedure completed.	The study was unclear regarding the impact of potential confounding factors (e.g., health history, other diseases, drug history, drug interactions, age at onset of illness, socioeconomic status, and the extent of support network) on the outcomes. Because of not reporting a sample size calculation, it was unknown if the study was adequately powered to identify statistically significant differences for all outcomes. The outcomes might have limited generalizability to patients with recurrent meningiomas because of a relatively small size, foreign-based, and single-centre study design. Assessing comparative effectiveness could be difficult because of the study design (i.e., a single-arm study) and the probability of unclear method of patient selection and the potentially high risk of selection bias.
Cardona et al. (2019)[14]	
The objective and patient characteristics were clearly described in the introduction and/or methods sections. The source of funding was clearly stated. The study used accurate (valid and reliable) outcome measures. The main findings were analyzed using the Kaplan–Meier method and the Log-Rank test with 95% CI. The results included actual probabilities. Toxicities were reported as AEs. The staff, places, and facilities associated with treatment were representative of the treatment received by the patients.	The risk of selection bias given that the treatment selection was based on factors such as AE profile, patient preference (oral or IV administration, etc.), and the availability of insurers. The study was unclear about treatment sequences and the number of patients in study groups (i.e., inconsistency in the information provided in the abstract and methods and/or results). Although toxicities were reported, it was unclear if all important AEs were considered. The role of several principal confounding factors and the method for adjusting survival curves for confounders were not described, therefor there was a high risk of confounding bias. Examples of confounding factors were crossover after progression or intolerability of the first line of medication, the low and variable number of patients in the sequences or lines of treatment, the variable time during which a patient received the medication, and the previous exposure to the medication. Limitations such as ambiguity in treatment sequences and the number of patients in study groups, as well as not considering the impact of several confounding factors might have affected the outcomes. No information was provided about the fidelity and completeness of patients' records. A sample size calculation was not reported in the article, and it was unknown if the study

Strengths	Limitations
	was adequately powered to identify statistically significant differences for all outcomes.

AEs = adverse events; CI = confidence interval.

Appendix 4: Main Study Findings

Note that this appendix has not been copy-edited.

Table 4: Summary of Findings by Outcome — PFS

Study citation and design	Method of measurement	End point	Result
Graillon et al. (2020)[7] Prospective, single-arm study	ITT population analysis	• PFS6 • PFS12 • Median PFS	N = 20 • PFS6 = 55% (95% CI, 31.3 to 73.5) • PFS12 = 30% (95% CI, 12.2 to 50.1) • Median PFS = 6.6 months (95% CI, 2.7 to 15.0)
	PP analysis	• PFS6 • PFS12	N = 18 • PFS6 = 61.1% (95% CI, 35.3 to 79.2) • PFS12 = 33.3% (95% CI, 13.6 to 54.5)
Cardona et al. (2019)[14] Retrospective cohort study	Results		
	No statistically significant difference between octreotide long-acting release in combination with everolimus (median PFS = 12.1 months; 95% CI, 9.2 to 21.1) and sunitinib (median PSF = 9.1 months; 95% CI, 6.8 to 16.8) (P = 0.43)		

CI = confidence interval; ITT = intention-to-treat; PFS = progression-free survival rate; PFS6 = PFS at 6 months; PFS12 = PFS at 12 months; PP = Per-protocol.

Table 5: Summary of Findings by Outcome — OS

Study citation and design	Method of measurement	Time point	Results
Graillon et al. (2020)[7] Prospective, single-arm study	ITT population analysis	• OS6 rate • OS12 rate	N = 20 • OS6 rate = 90% (95% CI, 65.6 to 97.4) • OS12 rate = 75% (95% CI, 50.0 to 88.7)
Cardona et al. (2019)[14] Retrospective cohort study	**Results**		
	• Median OS = 37.3 months (95% CI 28.5 to 42.1) • A statistically significantly longer OS in the group treated with the OE, Su, and Bev sequence vs. the group treated with the Su, OE, and Bev sequence (36.0 vs. 29.5 months) (P = 0.0001)		

Bev = bevacizumab; CI = confidence interval; ITT = intention-to-treat; OE = octreotide long-acting release in combination with everolimus; OS = Overall survival rate; OS6 = OS at 6 months; OS12 = OS at 12 months; Su = sunitinib.

Table 6: Summary of Findings by Outcome — Tumour Growth Rate

Study citation and design	Method of measurement	Time point	Result	P value
Graillon et al. (2020)[7] Prospective, single-arm study	MRI	Reduced tumour volume	A major decrease (> 50%): • 78% (21/27 tumours) at 3 months • 67% (12/18 tumours) at 6 months	0.0002 0.0003
		Long-term tumour growth control (i.e., > 2 years)	Observed in 3 patients	NA

MRI = MRI; NA = not applicable; NF2 = neurofibromatosis type 2; SSTR2A = somatostatin receptor subtype 2A.

Table 7: Summary of Findings by Outcome — Response Rate[a]

Study citation and design	Study findings
Graillon et al. (2020)[7] Prospective, single-arm study	• No complete or partial response was observed • Disappearance of 2 separate subcutaneous nodules in 1 patient under treatment
Cardona et al. (2019)[14] Retrospective cohort study	Stable disease and partial response in the first line of treatment • With octreotide long-acting release in combination with everolimus, 6 (43%) and 4 (28.6%), respectively • With sunitinib, 7 (63.6%) and 4 (36.4%), respectively

[a]Assessed according to the RANO criteria.[16]

Table 8: Summary of Findings by Outcome — Safety

Study citation and design	Study findings
Graillon et al. (2020)[7] Prospective, single-arm study	• 12 (55%) with stomatitis • Three patients with grade III AEs, leading to discontinuation of OE in one patient and everolimus alone in another patient.
Cardona et al. (2019)[14] Retrospective cohort study	• Some level of toxicity was observed in all patients treated with 2 treatment sequences (i.e., including 1) OE, sunitinib, and bevacizumab and 2) sunitinib, OE, and bevacizumab) • The most common side effects for OE were grade 1 or 2 fatigue in 12 (86%) and grade 1 or 2 edema in 2 (14%) patients • The most common AEs for sunitinib were grade 1 or 2 fatigue in 7 (73%) and hypothyroidism in 2 (18%) patients • Grade 3 fatigue leading to dose reduction was reported in 3 patients treated with sunitinib • Deep vein thrombosis was reported in 2 patients treated with bevacizumab.

AEs = adverse events; OE = octreotide long-acting release in combination with everolimus.

Appendix 5: References of Potential Interest

Note that this appendix has not been copy-edited.

The following publications were identified because they provide additional information associated with the topic of this report (i.e., previous CADTH reports) or additional guidance on ST or multidisciplinary therapy for relapsed/refractory meningioma.

Previous CADTH Reports

Octreotide Long-Acting Release and Everolimus for Recurrent Meningiomas. Ottawa (ON): CADTH. 2022. https://www.cadth.ca/octreotide-long-acting-release-and-everolimus-recurrent-meningiomas Accessed 2022 Nov 3.

Combination Therapy for the Treatment of Central Nervous System Malignancies: Clinical Effectiveness and Guidelines. Ottawa (ON): CADTH. 2019. https://www.cadth.ca/combination-therapy-treatment-central-nervous-system-malignancies-clinical-effectiveness-and Accessed 2022 Nov 3.

Review Articles

Brastianos PK, Galanis E, Butowski N, et al. Advances in multidisciplinary therapy for meningiomas. *Neuro Oncol*. 2019;21(Suppl 1):i18-i31. PubMed

Dasanu CA, Alvarez-Argote J, Limonadi FM, Codreanu I. Bevacizumab in refractory higher-grade and atypical meningioma: the current state of affairs. *Expert Opin Biol Ther*. 2019;19(2):99-104. PubMed

Dasanu CA, Samara Y, Codreanu I, Limonadi FM, Hamid O, Alvarez-Argote J. Systemic therapy for relapsed/refractory meningioma: Is there potential for antiangiogenic agents? *J Oncol Pharm Pract*. 2019;25(3):638-647. PubMed

Zhao L, Zhao W, Hou Y, et al. An Overview of Managements in Meningiomas. *Front Oncol*. 2020;10:1523. PubMed

Graillon T, Tabouret E, Chinot O. Chemotherapy and targeted therapies for meningiomas: what is the evidence? *Curr Opin Neurol*. 2021;34(6):857-867. PubMed

Maggio I, Franceschi E, Tosoni A, et al. Meningioma: not always a benign tumor. A review of advances in the treatment of meningiomas. *CNS Oncol*. 2021;10(2):Cns72. PubMed

McFaline-Figueroa JR, Kaley TJ, Dunn IF, Bi WL. Biology and Treatment of Meningiomas: A Reappraisal. *Hematol Oncol Clin North Am*. 2022;36(1):133-146. PubMed

Pellerino A, Bruno F, Palmiero R, et al. Clinical Significance of Molecular Alterations and Systemic Therapy for Meningiomas: Where Do We Stand? *Cancers (Basel)*. 2022;14(9). PubMed

In Vitro Study

Graillon T, Romano D, Defilles C, et al. Octreotide therapy in meningiomas: in vitro study, clinical correlation, and literature review. *Journal of Neurosurgery*. 2017;127(3):660-669. PubMed