Medical management of meningiomas

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Practice Points

- Small and asymptomatic meningiomas can often be observed and treated if they grow significantly or cause symptoms. However, if they present in a more aggressive or symptomatic form they require intervention.
- The efficacy and role of surgery and radiation in the treatment of meningiomas has been well established.
- When meningiomas recur despite prior therapy with surgery and radiation, or when they are inoperable, a trial of medical therapy often ensues, although the data behind such therapies is modest at best.
- Cytotoxic agents appear to have minimal efficacy and may have toxicity out of proportion to their anti-tumor effects.
- The use of hydroxyurea and somatostatin is supported by cancer guidelines, but the evidence behind such use is weak.
- Current investigations are looking at targeted therapies, particularly those targeting receptor tyrosine kinases, such as VEGF, or intracellular targets, as potential candidates for improving progression-free and overall survival in patients with recurrent or progressive meningiomas. While initial studies look promising, further data is required to better determine level of efficacy.

SUMMARY The efficacy of surgery and radiation has been well validated in the treatment of meningiomas, with efficacy depending on tumor pathology, size, symptomatology and rate of progression. The role of medical therapy has the least amount of data but is being increasingly investigated for tumors that are inoperable or those tumors that recur and/or progress despite standard therapy. In this review, current data on the use of chemotherapeutic agents in the management of meningiomas will be reviewed, including cytotoxic, biologic, targeted molecular and hormonal agents.

Meningiomas represent the most common primary brain tumor found in adults, according to the Central Brain Tumor Registry of the United States (CBTRUS) [101]. Their clinical

presentation and course can vary drastically, from asymptomatic lesions that are found incidentally and grow very slowly (if at all), to large invading tumors that can encompass or

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compress vital structures. To represent and classify this heterogeneity within the class of meningiomas, WHO classified these tumors based on histologic criteria, dividing these tumors into three grades [1]. The WHO classification system includes the incidence of mitoses, as well as the degree of nuclear atypia, when subdividing these tumors into their respective grades. The most recent update published in 2007 includes the presence of brain invasion as a criterion for atypia [1]. The majority of meningiomas are classified as grade I meningiomas, otherwise referred to as ‘benign’, which represent approximately 80–85% of meningiomas; grade I have the lowest risk of recurrence following resection with or without subsequent radiation. Grade I meningiomas have nine histologic subtypes (Box 1). Grade II (atypical) and grade III (malignant) meningiomas represent higher-grade tumors with features of histologic aggressiveness, resulting in a higher rate of recurrence despite standard therapy with surgery and radiation; they also have histologic subtypes (Box 1).

Standard treatment

Surgical resection remains the optimal initial treatment approach in the management of meningiomas. In 1957, Simpson published what are now referred to as the ‘Simpson Criteria’, where he correlated the extent of tumor resection, dural attachments and presence of any hyperostotic bone to local recurrence risk. He

found five distinct grades of resection, which correlated well with specific recurrence rates [2]. While gross total resection is ideal and is associated with a decreased risk of recurrence, the degree of surgical success depends on the tumor size, location and invasiveness/proximity to other structures. The extent of resection has been directly associated with risk of recurrence [3]. Grade I tumors that are incompletely resected, due to their anatomic location near critical structures, often recur despite their ‘benign’ label. Even gross totally resected grade I tumors have a 12% recurrence rate within 5 years of resection and 19% within 20 years [3,4]. Recurrence rates in grade II tumors following gross total resection are between 29 and 40% within 5 years of resection [5]. For grade III tumors following gross total resection, a recurrence rate as high as 80% has been reported, although the addition of radiation therapy to the gross total resection lowered the recurrence rate to 57% [6]. Following resection of malignant meningiomas, post-surgical radiation is recommended and is also often recommended for tumors considered inoperable or subtotally resected [7]. The role of radiotherapy following gross total resection of atypical meningiomas has been a controversial topic, although preliminary data seem to support its role in upfront treatment. Aghi *et al.* performed a retrospective review of 108 atypical meningiomas, looking at long-term recurrence rates [8]. They found high recurrence rates without upfront radiation, with most recurrences occurring within 5 years of the resection and being associated with numerous reoperations and shortened survival, suggesting a potential role for upfront radiotherapy, although a prospective study is required to better delineate this controversial issue [8]. There have been other recent retrospective studies demonstrating a role for upfront radiotherapy in the treatment of atypical meningiomas, although treatment modalities varied [9]. Radiotherapy modalities utilized in the treatment of meningiomas includes single-fraction stereotactic radiosurgery, hypofractionated stereotactic radiotherapy and conventional external beam radiotherapy. There appears to be a growing role for stereotactic radiosurgery or hypofractionated stereotactic radiotherapy in the treatment of inoperable or subtotally resected meningiomas, in an effort to spare patients the toxicity attributed to external beam radiotherapy and improve tumor control with higher dosages per fraction. One large retrospective review

Box 1. WHO classification of meningioma subtypes.

Grade I

- Meningoepithelial
- Fibrous (fibroblastic)
- Transitional (mixed)
- Psammomatous
- Angiomatous
- Microcystic
- Secretory
- Lymphoplasmacyte-rich
- Metaplastic

Grade II

- Clear cell
- Chordoid
- Atypical
- Brain invasion with otherwise grade I features

Grade III

- Anaplastic/malignant
- Papillary
- Rhabdoid

concluded that post-operative radiotherapy for residual tumor following surgery should be utilized only when the residual disease cannot be managed with radiosurgery [10].

The role of medical therapy in the treatment of these tumors remains limited. If or when meningiomas recur or progress, their subsequent treatment would ideally include medical therapy beyond radiation and surgery, especially when those are no longer options. Those tumors that are labeled inoperable due to their location or proximity to vital structures often also require medical management. The optimal medical therapeutic strategy or salvage therapy remains to be determined, although many agents have been tried and others are being investigated, including hormonal, cytotoxic and biologic agents, as will be subsequently discussed.

Cellular & molecular biology of meningiomas

In trying to better elucidate the optimal medical therapies for these tumors, genetic and signal transduction pathways have been delineated in the hope of providing potential targets for therapeutic approaches. All pathologic meningioma subtypes are thought to arise from a prostaglandin D synthase-positive meningeal precursor cell [11]. Loss of heterozygosity of chromosome 22, with the *NF2* gene being the primary target, has been associated with approximately 50% of sporadic meningiomas and most meningiomas in *NF2* patients [12,13]. The merlin protein is encoded by the *NF2* gene and has been implicated in the regulation of growth and motility of cells, the loss of which is thought to contribute to meningioma formation [14].

The enhanced expression of several growth factor receptor/kinases has been implicated in meningioma development and progression. In meningioma cells, widespread enhanced expression of EGF receptors has been noted [15,16]. *In vitro* studies have shown that EGF receptors are stimulated by both EGF and TGF- α , resulting in meningioma cell proliferation [17,18]. Additionally, meningioma aggressiveness has been positively correlated with increased TGF- α immunoreactivity in meningeal cells [19]. The expression and activation of PDGF receptor (PDGFR) has also been associated with meningiomas [20,21], the increased expression of which appears to be unrelated to histologic grade [22]. Activation of PDGFR is thought to result in aberrant cell signaling through either one of

two pathways: PI3K/AKT or RAS/MAPK pathways [23,24]. These pathways have been shown to result in growth stimulation and inhibition of apoptosis, resulting in tumor formation or growth. GTPase RAS protein acts as the intermediate step; RAS is stimulated upon receptor activation and subsequently activates the aforementioned pathways [25]. This has led to investigations looking at tyrosine kinase inhibitors as medical therapy for meningiomas, which will be discussed later. IGF-II has also been shown to have increased expression in invasive progression of meningiomas [26].

Increased expression of androgen receptors has been found in meningiomas, resulting from initial observations that meningiomas are more prevalent in women, with a high incidence during their reproductive years. Additionally, both epidemiological studies and case reports have shown either growth or development of meningiomas with administration of hormonal agents, although this correlation has been controversial [27–30]. Progesterone receptors have been found in approximately two-thirds of meningiomas, while estrogen receptors are found in only 10% of meningeal tumors. Progesterone receptors are most commonly in benign, or grade I, meningiomas, as opposed to the more aggressive subtypes [12].

Treatments

■ Cytotoxic agents

Cytotoxic agents have shown limited efficacy in the treatment of progressive or recurrent meningiomas. A variety of agents, including temozolomide, dacarbazine, adriamycin, ifosfamide and irinotecan (CPT-11), have been investigated in the treatment of meningiomas, with minimal if any efficacy, but significant toxicity [31,32]. Temozolomide is an oral alkylating agent approved for the treatment of malignant gliomas. Temozolomide's use in the treatment of meningiomas was investigated in a Phase II study where 16 patients with refractory meningioma were prospectively enrolled. Of the 16 patients enrolled in the study, zero patients demonstrated a radiographic complete or partial response to temozolomide therapy. Additionally, the study showed a median survival of only 7.5 months (range: 4–9 months), with a median time to progression of 5 months (range: 2.5–5 months) [33]. It has been hypothesized that temozolomide's disappointing efficacy in these tumors may be due to the DNA repair enzyme

*O*⁶-methylguanine-DNA-methyltransferase, the methylation of which predicts response to therapy with alkylating agents in malignant gliomas; however, *O*⁶-methylguanine-DNA-methyltransferase promoter methylation is rare or absent in benign meningiomas [34].

Other cytotoxic agents tried in meningiomas include irinotecan, an intravenous antineoplastic agent (topoisomerase inhibitor) used in multiple systemic cancers, particularly colon cancer, as well as in gliomas. In preliminary *in vitro* studies, irinotecan seemed to inhibit meningeal cell growth [35]; however, a Phase II trial failed to demonstrate clinical efficacy of irinotecan in the treatment of recurrent/progressive meningiomas [36]. A combination of cyclophosphamide, adriamycin and vincristine (CAV) demonstrated a modest survival benefit when 14 patients with malignant meningioma, all of whom had undergone surgical resection followed by radiation therapy, were treated with three to six cycles of the CAV regimen (three cycles for those who had achieved gross total resection surgically and six cycles for those in whom only subtotal resections could be performed). The median time to tumor progression was 4.6 years (2.2–7.1 years) and a modest survival benefit was found, with a median survival of 5.3 years (2.6–7.6 years). While CAV may demonstrate moderate efficacy in terms of survival, the patients who received the regimen experienced significant toxicity, particularly myelosuppression, with three of the patients requiring early discontinuation of treatment due to their toxicities [37]. Aside from the toxicity, there is the question of whether the regimen truly adds a survival benefit. A requirement for the study was preceding treatment with surgery and radiation; hence, one cannot be certain as to which aspect of the treatment regimen to attribute the survival benefit.

Hydroxyurea has become a standard therapy in the treatment of meningiomas refractory to surgery and radiation after some initial promising data; however, subsequent retrospective data has called its efficacy into question. Hydroxyurea is an oral ribonucleotide reductase inhibitor that acts via arrest of the S phase of the cell cycle, thereby inducing apoptosis and theoretically arresting meningioma cell growth [38]. Initially, a small study of only four patients with recurrent and unresectable meningiomas demonstrated potential efficacy. Out of the four patients receiving treatment with hydroxyurea, three patients demonstrated a radiographic response (15–74%

shrinkage on MRI), while the fourth patient demonstrated stable disease [39]. This prompted a prospective study of 17 patients, of whom 16 were evaluable for response. Of the 16 patients available for response evaluation, 14 patients responded with stable disease (from 20 to ≥144 weeks, median 80 weeks) and two patients had progressive disease after only 10 weeks of therapy [40]. Cytostatic activity was attributed to hydroxyurea after subsequent smaller studies showed disease stability with hydroxyurea treatments [41,42]. This observed cytostatic response, while initially attributed to hydroxyurea activity, may actually represent the natural course of these tumors. This theory was supported by a subsequent study in 2004 that enrolled 12 patients with regrowing, non-malignant meningiomas, whom received 2 years of continuous therapy with hydroxyurea. Median time to progression was 13 months in nine patients. Of the other three patients, one showed a radiographic response with subsequent disease stabilization, while the other two patients had to discontinue treatment due to hematologic toxicity [43]. More recently, Chamberlain published two retrospective case series of meningiomas treated with hydroxyurea. Neither study demonstrated efficacy of hydroxyurea against meningiomas suggesting no role for this agent [44,45].

Investigators have also looked at the efficacy of combining hydroxyurea with radiotherapy in recurrent meningiomas. In one study that prospectively enrolled 21 patients with recurrent or progressive meningiomas receiving combination therapy of hydroxyurea during radiation therapy, 14 patients demonstrated disease stabilization with an additional three patients showing radiographic and symptomatic improvement. The 1-year progression-free survival (PFS) was found to be 84% with that at 2 years being 77% [46]. Patients appeared to tolerate the combination therapy well, but whether this combination therapy is superior to radiation alone remains to be determined and would require a prospective, randomized study.

One explanation for the poor efficacy of cytotoxic agents in the medical management of meningiomas may be related to drug-resistance proteins and transporters known to contribute to resistance to chemotherapeutic agents used in the treatment of systemic malignancies. Membrane efflux pumps, drug detoxification and alteration in drug target specificity have all been implicated in drug resistance. P-glycoprotein,

multidrug resistance-associated protein and lung resistance-related protein are membrane transport proteins that have been shown to be consistently expressed in all grades of meningioma [47]. Topoisomerase II α is an enzyme related to DNA repair and proliferation [48] that has also demonstrated constant expression in meningiomas of all grades. While protective in normal cells, particularly against toxic compounds, in malignant cells they lead to drug resistance. Interestingly, P-glycoprotein, lung resistance-related protein and topoisomerase II α were found not only in neoplastic vessels, but also normal vessels, leading to the hypothesis that they may also contribute to the role of the blood–brain barrier or at least prevent optimal drug penetration into meningiomas, since the blood–brain barrier is thought not to be an issue. When recurrent and irradiated meningiomas were specifically studied with regard to the presence of these proteins, there did not appear to be a difference in expression [47]. Perhaps inhibition of these proteins may lead to greater efficacy of chemotherapeutic agents in the management of meningiomas, although further research in this area is required.

■ Biologic agents

Utilizing this knowledge of androgen receptor prevalence, hormonal agents have been investigated as possible therapeutic agents in the treatment of meningiomas, but with limited success. Estrogen receptor inhibitors have proven ineffective in inhibition of meningioma growth, as may be expected given the low incidence of estrogen receptors in meningiomas, in contrast to the prevalence of progesterone receptors. An initial Phase II study of 19 patients only saw a partial or minor response to tamoxifen therapy in three of the study participants [49].

In an effort to target the more prevalent progesterone receptors, mifepristone (RU486), a progesterone receptor inhibitor, has been investigated. Several small studies claimed a modest benefit. However, a large, prospective, randomized multicenter study refuted these initial claims. This trial studied 180 patients, who were randomized to either daily mifepristone or placebo; there was no demonstrable benefit to mifepristone over placebo [50]. A common criticism of the mifepristone studies is that most patients enrolled had grade II or III meningiomas, while it is well known that progesterone receptors are much more common in grade I tumors. Therefore, it is possible mifepristone

may still prove efficacious if tested in patients with grade I tumors, where the target receptors for the drug are much more likely to be expressed.

Both IFN- α and somatostatin represent biologic agents thought to have potential efficacy in the treatment of recurrent or progressive meningioma. IFN- α has been studied in the treatment of these tumors owing to initial evidence suggesting IFN- α therapy may lead to inhibition of meningioma cells *in vitro* [51]. This is thought to be due to IFN- α 's properties of antiproliferation, immunomodulation and anti-angiogenesis [52,53]. Similarly to prior therapies discussed, while initial evidence looked promising, the studies that followed have been less so. Chamberlain and Glantz published a Phase II study of patients with recurrent, treatment-refractory, WHO grade 1 meningiomas who were prospectively treated with IFN- α [53]. Of the 35 patients enrolled, neither complete nor partial radiographic responses were observed. The primary end point was PFS, which was found to be 54% at 6 months and 31% at 12 months, with a median time to progression of 7 months (range: 2–24 months). Unfortunately, these studies lack control data, which, in conjunction with modest, at best, efficacy, does not adequately answer the question of the role of IFN- α in the treatment of meningiomas [54].

Somatostatin has been investigated in the medical management of meningiomas after it was found that somatostatin receptors are present in almost 90% of meningiomas. This led to *in vitro* studies demonstrating inhibition of meningioma cell proliferation with somatostatin therapy [55]. Octreotide scintigraphy has been used to identify patients whose tumors are somatostatin receptor positive as potential candidates for somatostatin therapy. This modality was used to enroll 16 patients to prospectively receive somatostatin therapy for their recurrent meningiomas. The 6-month PFS was found to be 44%, with partial radiographic response achieved in 31% of patients, stable disease in 31% and progressive disease in 38% [56]. These prospective results indicate a potential role for somatostatin in patients in whom octreotide scintigraphy demonstrates somatostatin receptor positivity, particularly given the minimal toxicity of somatostatin. The limitation of this study is a mixed group of meningiomas, so small numbers for analysis based upon tumor subtype.

Octreotide is a somatostatin receptor agonist

that has been studied in recurrent meningiomas. A Phase II study failed to show significant efficacy radiographically; however, octreotide scintigraphy demonstrating somatostatin receptor positivity was not an inclusion criteria for enrollment, leaving open the question as to whether the correct patient population was targeted in this study [57]. Similarly, pasireotide long-acting release, a long-acting somatostatin analog, was studied in a single-arm Phase II trial based on the hypothesis that perhaps pasireotide long-acting release will prove more efficacious than related agents, owing to its higher binding affinity. Unfortunately, again, an objective radiographic response was not seen in 22 patients evaluable for response, with a median PFS of only 16 weeks [58]. Johnson *et al.* conducted a Phase II study of subcutaneous octreotide in 11 patients with recurrent meningioma and one patient with meningeal hemangiopericytoma. Similarly, no radiographic responses were observed, with 11 of the 12 patients experiencing disease progression, with a median time to progression of 17 weeks [57]. Again, while well tolerated, an objective tumor response was not observed.

■ Targeted molecular therapies

As previously discussed, dysregulated or aberrant cell signaling pathways have been implicated in meningioma cell proliferation, survival, invasion and angiogenesis [59]. Current research into medical therapies for meningiomas focuses on agents targeting different aspects of these pathways, namely PDGF, VEGF and other components of the MAPK pathway (Table 1). Imatinib mesylate, a PDGFR inhibitor, was investigated in patients with recurrent meningiomas, based on the knowledge that PDGF is frequently expressed in meningiomas of all grades and that there appears to be an autocrine loop. Patients with tumors of all three grades received imatinib. Nineteen patients were evaluable for a response, which found a median PFS of only 2 months (range: 0.7–34 months), with nine patients with stable disease at first scan and ten patients demonstrating progression. While imatinib was well tolerated, it did not appear to have significant efficacy in regards to PFS nor radiographic response in recurrent meningiomas [60]. Horak *et al.* conducted a retrospective analysis of imatinib used in nine patients with recurrent meningioma demonstrating immunohistochemical staining of PDGFRs [61]. Of these nine patients, seven had stable radiographic disease and two presented

with progression at the time of the first scan after 3 months. While a radiographic response was not observed, they found the 6-month PFS to be 66.7%, with an overall median PFS of 16 months [61]. This review suggested a potential role for imatinib in preselected patients demonstrating PDGFR positivity. A combination Phase II study enrolling 21 patients, looked at giving imatinib in combination with hydroxyurea. Similar to the imatinib monotherapy trial, no radiographic responses were seen, with 14 patients showing stable disease and the other seven patients with progressive radiographic disease. Efficacy with regard to PFS at 6 months seemed to be modestly improved compared with that of imatinib monotherapy: 61.9% in grade I; 87.5% in grade II; and 46.2% in grade III meningiomas [62]. Combination therapy did not seem to confer greater toxicity, but efficacy remains limited.

The EGF receptor inhibitors gefitinib and erlotinib have been investigated in patients with recurrent meningiomas based on their observed enhanced expression and signaling via proliferation pathways, similar to that of PDGFRs. Norden *et al.* prospectively enrolled 25 patients with recurrent meningioma to receive either gefitinib or erlotinib [63]. They found the 6-month PFS to be 25% for benign histologies and 29% for those tumors with atypical or malignant histologies [63]. All patients appeared to tolerate therapy, but efficacy remained limited.

VEGF inhibitors have been tried with varying degrees of success in the treatment of meningiomas. Their use is based upon the well-known hypervascularity associated with meningiomas, the VEGF-driven angiogenesis that is thought to contribute to the continued growth of these tumors [64,65] and the level of VEGF expression that appears to correlate with tumor grade [66,67]. Several case reports have shown radiographic improvement with VEGF inhibitors [68], which have prompted prospective VEGF trials in meningiomas. An additional potential therapeutic benefit of VEGF inhibitors in meningioma treatment may be the reduction of peritumoral edema, which contributes significantly to the symptomatology of many proliferating meningiomas [69]. Lou *et al.* recently released their retrospective review of 14 patients with recurrent meningioma treated with bevacizumab, a VEGF monoclonal antibody [70]. Four of the patients were treated with bevacizumab monotherapy, while the other ten patients received bevacizumab in combination with etoposide and either sirolimus

Table 1. Comparison of current data on targeted agents.

Study (year)	Agent	Mechanism of action	All-grade tumors	Grade II/III	Radiographic response	Ref.
Wen <i>et al.</i> (2009)	Imatinib	PDGFR inhibitor	PFS-6: 30% mPFS: 2 mo	PFS-6: 0% mPFS: 2 mo	50% SD	[60]
Norden <i>et al.</i> (2010)	Gefitinib/erlotinib	EGFR inhibitor	PFS-6: 28% mPFS: 2.5 mo mOS: 23 mo	PFS-6: 29% mPFS: 4 mo OS: 33 mo	32% SD	[63]
Reardon <i>et al.</i> (2012)	Imatinib and HU	–	PFS-6: 61.9% mPFS: 7.0 mo	PFS-6: 46.2% mPFS: 5.3 mo mOS: 20.9 mo	31% SD	[62]
Kaley <i>et al.</i> (2009)	Sunitinib	Tyrosine kinase receptor inhibitor	–	PFS-6: 36% mPFS: 4.6 mo	61% SD 3.6% PR	[75]
Raizer <i>et al.</i> (2010)	PTK-787	VEGFR and PDGFR inhibitor	PFS-6: 60.0% mPFS: 7.3 mo	PFS-6: 64.3/37.5% mPFS: 7.6/3.6 mo OS: 26/23 mo	71% SD 5% PR	[73]
Lou <i>et al.</i> (2012)	Avastin	VEGF antibody	PFS-6: 85.7% mPFS: 17.9 mo	PFS-6: 87.5% mPFS: 17.9 mo	–	[76]

EGFR: EGF receptor; HU: Hydroxyurea; mo: Months; mOS: Median overall survival; mPFS: Median progression-free survival; OS: Overall survival; PDGFR: PDGF receptor; PFS-6: 6-month progression-free survival; PR: Partial response; SD: Stable disease; VEGFR: VEGF receptor.

or temozolomide. The 6-month PFS in patients with grade II or grade III meningiomas was found to be 87.5%, with a median PFS of 17.9 months. There also seemed to be a slightly better outcome in those patients receiving bevacizumab in combination with another chemotherapeutic agent [70]. Nayak *et al.* also performed a retrospective review of 15 patients with grade II or III meningiomas treated with bevacizumab across four institutions. Stability was the best response achieved. They found a median PFS of 26 weeks, with a 6-month PFS rate of 43.8% [71]. The improved PFS in the Reardon *et al.* study may likely be attributed to their combination therapy with other chemotherapeutic agents or patient selection.

In an effort to target both VEGF and PDGFRs, PTK-787 has been investigated in grade II and III meningiomas previously treated with both radiation and surgery. In a Phase II trial, 21 patients were enrolled to receive treatment with PTK-787. A total of 21 of the 25 patients enrolled were evaluable for response; there was one partial response, 14 with stable disease and six with progressive disease. For grade II patients the 6-month PFS was 64.3%, median PFS was 7.6 months and overall survival was 26.0 months; for grade III patients the 6-month PFS was 37.5%, median PFS was 3.6 months and overall survival was 23 months [72,73] [RAIZER JJ *ET AL.* A PHASE II TRIAL OF PTK-787 IN RECURRENT OR PROGRESSIVE RADIATION AND SURGERY REFRACTORY MENINGIOMA (2013), MANUSCRIPT IN PREPARATION]. Sunitinib is also an inhibitor of both VEGF and PDGFRs, which has been studied in grade II

and III recurrent meningiomas. A slightly longer median PFS of 5.1 months was found, with the best response seen as disease stability in three of the ten patients [74]; however, further studies of both of these agents are required to determine their role in the treatment of these tumors.

Conclusion

The field of neuro-oncology continues to search for the optimal medical therapy in the treatment of meningiomas, particularly when faced with the challenge of recurrent or inoperable tumors. As we better understand the biology of these tumors, we are more likely to develop an effective therapy, especially if we can use tissue profiling as a guide to choosing an appropriate therapy. At this point in time, there is only very weak evidence to suggest the use of cytotoxic agents, particularly given their toxicities. Hormonal agents have not been shown to be effective, although perhaps progesterone inhibitors may have a potential role in benign tumors, but this has yet to be established. Biologic agents, particularly somatostatin, may play a role in tumors demonstrating somatostatin receptor positivity on octreotide scintigraphy, but further studies are required. With regard to targeted molecular agents, VEGF and PDGF inhibitors (or other multitargeted agents) may be the most promising, with further studies currently ongoing. Given the lack of definitive data relating to the efficacy of medical therapies in the treatment of meningiomas, the future will be determined by new studies and their results, with targeted molecular agents appearing most promising at this point in time. Defining

benchmarks of efficacy and response criteria are essential and are being developed by the Response Assessment in Neuro-Oncology (RANO) group.

In clinical practice, the author's recommendation for meningiomas requiring medical therapy would be to enroll the patient in a clinical trial whenever possible so as to better answer these questions. Designing trials that allow presurgical treatment would be beneficial in determining drug levels and also whether chosen targets are affected. If a trial is not available or not feasible for the individual patient, then perhaps one could consider octreotide scintigraphy to determine if somatostatin may be a viable option, otherwise any of the agents discussed with the best activity could be considered.

Future perspective

As studies continue in an effort to optimize medical management of meningiomas, as a field we face challenges in study designs. Initially, many studies were not subdivided by tumor grade, although we know that receptor positivity varies greatly between grades and, therefore, it is probable that the optimal medical agents relating to target availability will also vary. After accrual of enough patients in the respective tumor grades (grade I and grade II/III, although the later might also be split into separate groups), we also must decide as a field which primary end points we choose to define efficacy of an agent. Some studies have looked at radiographic response, while others have looked at either PFS or overall survival, as the end points to delineate efficacy. If we are to compare trials and agents, the method of determining efficacy must become uniform. The RANO group will be submitting two

manuscripts to address these issues shortly [RANO GROUP, PERS. COMM.] and, in addition, designing trials where tissue can be assessed would be of value in understanding treatment successes and failures.

While Simpson grading has been well established as correlating with recurrence rates, it can be difficult to recognize the difference between Simpson grades 1–3 based on MRI alone. Simpson grades 1–3 may appear similarly on post-operative MRI, but clearly each grade behaves differently in terms of recurrence. Additionally, the salutatory growth of meningiomas has been well reported, which may confound PFS times during the plateau phase of growth. While it may be difficult to address these issues in study design, they must be kept in mind when interpreting study results; importantly, the Simpson criteria are for surgical resection.

The medical management of meningiomas represents a deep unmet need in the field of neuro-oncology. Multicenter prospective trials are required for adequate accrual, particularly as we gain more information with regard to the molecular biology of the tumors, potentially employing combination therapy, as is being trialed in the more prevalent glioma studies.

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