EDITORIAL

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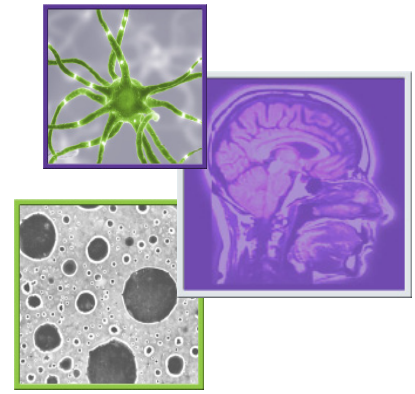
Is there effective systemic therapy for recurrent surgery- and radiation-refractory meningioma?



Marc C Chamberlain*

"...there is a perception by the neuro-oncology community that the systemic treatment of recurrent meningioma following failure of surgery and radiotherapy is futile."

Meningiomas are the most common intracranial neoplasm, constituting 20–30% of all primary brain tumors [1–8]. WHO categorizes meningiomas into three grades: grade 1, so-called benign meningiomas; grade 2, atypical meningiomas; and grade 3, anaplastic meningiomas. The majority of meningiomas (>80%) are WHO grade 1, in which complete surgical resection results in prolonged disease-free survival or cure. By contrast, WHO grade 2 and 3 (high-grade) meningiomas, despite initial surgical resection often accompanied by radiotherapy, frequently recur and require re-treatment primarily with re-resection or re-irradiation. Notwithstanding the utility of surgery and radiotherapy for the primary treatment of meningioma, there are a minority of patients in whom alternative systemic therapies are used in instances of recurrent meningioma. There are, however, very few systemic therapies that appear to have activity in recurrent meningioma [9–30]. The CNS National Comprehensive Cancer Network guidelines, based on consensus expert opinion, suggest as treatment options for recurrent meningioma hydroxyurea (HU), IFN-α or Sandostatin® LAR® (Novartis, Basel, Switzerland), a somatostatin analog [8]. The National Comprehensive Cancer Network systemic therapy guidelines for recurrent meningioma are, however, based on very limited literature [9–30].

There is a single study of systemic therapy for newly diagnosed anaplastic meningioma (WHO grade 3) that was inconclusive regarding the benefit of adjuvant chemotherapy. The majority of opinions conclude at present that there are insufficient data to suggest a role for cytotoxic chemotherapy in the treatment of either newly diagnosed or recurrent meningioma [1,2,4,5,7,28]. The single exception is with respect to the use of HU for recurrent meningioma, for which there is the largest data-set relating to cytotoxic chemotherapy [9–16,26,29]. Patients in these studies were not stratified with respect to tumor grade. Additionally, prior treatment varied and, in the majority of patients, radiotherapy had not been administered or was administered concurrently. Consequently, assessing the response to HU as a single agent is problematic.

"How to define activity against meningioma is challenging as the limited literature is inconsistent with respect to outcome end points and predominantly comprised of retrospective studies."

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The predominance of females and expression of progesterone and estrogen receptors (70 and 30% positivity, respectively) in meningioma have suggested that meningioma growth may be hormone dependent [1,2,5,7]. Consequently, early clinical trials of recurrent meningioma utilized a variety of hormonal agents. Megestrol acetate (Megace®), an oral progesterone agonist, was used in a small trial of nine patients with no observed response [1–7]. The Southwest Oncology Group (SWOG) completed a study of mifepristone (RU-486), a progesterone antagonist, for unresectable WHO grade 1 meningiomas (198 total patients of whom 160 were evaluable) [27]. The results did not support a role for RU-486 as compared with placebo (median progression-free survival [PFS] was 10 months in the RU-486 arm and 12 months in the placebo arm). In addition, SWOG reported on an exploratory Phase II trial of 21 meningioma patients treated with oral tamoxifen, an estrogen receptor antagonist that proved to be inactive [1–7].

IFN-α has been found to inhibit the growth of cultured human meningioma cell lines *in vitro* [25]. Four small reports, two in abstract form only, have been published [25]. In the largest report, 35 patients with recurrent unresectable and previously irradiated WHO grade 1 meningiomas were treated [25]. Although no radiographic responses were seen, 74% demonstrated stable disease with a median PFS of 7 months (6- and 12-month PFSs were 54 and 31%, respectively). Median overall survival was 8 months (range: 3–28 months), suggesting that IFN-α may be an active agent for recurrent low-grade meningioma. There has been no comparable trial of IFN-α in patients with recurrent high-grade meningioma.

The molecular pathogenesis of meningioma is poorly defined and, consequently, the critical molecular changes that determine meningioma growth remain to be characterized [1,7,31]. Nonetheless, it is known that several growth factors are overexpressed, including PDGF, EGF and VEGF. These growth factors, their receptors and signal transduction pathways have been implicated in meningioma tumor biology, but their relative contribution is largely conjectural [17–22,30]. As a result, the most important molecular targets for meningioma-targeted therapy remain uncertain.

The majority of meningiomas express somatostatin receptors, providing a molecular rationale for utilizing long-acting somatostatin analogs for therapeutic and diagnostic purposes [24]. In the largest trial of somatostatin use in meningiomas, 16 patients with recurrent meningiomas (progressive after prior surgery and radiotherapy) shown to overexpress somatostatin receptors by octreotide scintigraphy were treated with monthly long-acting somatostatin (Sandostatin LAR) [24]. A total of 31% of patients demonstrated a partial radiographic response and 44% achieved PFS at 6 months with minimal toxicity. New somatostatin analogs with higher affinity may offer a novel, relatively nontoxic alternative treatment for patients with recurrent meningiomas. Pasireotide (SOM230C) is an intramuscularly administered, long-acting somatostatin analog with a wider somatostatin receptor spectrum (including subtypes 1, 2, 3 and 5) and higher affinity (particularly for subtypes 1, 3 and 5) than the sustained-release somatostatin described above. A Phase II trial for patients with recurrent or progressive meningiomas has recently opened and is accruing patients [23].

PDGF is a canonical driver of cell proliferation in normal development and cancer. The majority of meningiomas of all histological grades express PDGF ligand and the PDGF-β receptor. The North American Brain Tumor Consortium conducted a Phase II study of imatinib, a PDGF receptor inhibitor, in patients with recurrent meningiomas [20,21]. Patients were stratified into two cohorts: benign meningiomas; or atypical and malignant meningiomas. A total of 23 patients were enrolled on the study and, although the imatinib treatment was well-tolerated, there was minimal activity. Nineteen of the 23 patients were evaluable for response, of which ten progressed at first evaluation, and nine were stable; there were no radiographic responses. For both cohorts of patients, median PFS was 2 months and 6-month PFS was 29.4%. In the cohort of benign meningioma (WHO grade 1), median PFS was 3 months and 6-month PFS was 45%. For higher-grade meningioma (atypical and malignant), median PFS was 2 months and 6-month PFS was 0%.

The EGF receptor (EGFR) is overexpressed in more than 60% of meningiomas [1–7]. The North American Brain Tumor Consortium conducted two trials of EGFR inhibitors in recurrent meningiomas using either gefitinib (500 mg/day; Iressa™, AstraZeneca, London, UK) or erlotinib (150 mg/day; Tarceva®,

Genentech, CA, USA) [22]. A total of 25 patients were entered on the trial. In both studies, the drugs were well tolerated; the main toxicities were the expected adverse effects of rash and diarrhea seen with EGFR inhibitors. Nonetheless, there were no objective responses and 6-month PFS was 25%. Based on the results of this study, neither EGFR inhibitor appears to have significant activity against recurrent meningioma. At present there are no data regarding EGFR-directed monoclonal antibodies, such as cetuximab or panitumumab, in the treatment of meningioma.

Of the patients undergoing targeted therapy for recurrent meningioma who have been evaluated and reported to date, the most robust signal has been seen with angiogenic inhibitors targeting the VEGF signaling pathway, another growth factor pathway upregulated in meningiomas [17–19,30]. Two strategies have been employed targeting this pathway; bevacizumab (VEGF ligand-directed therapy) and VEGF receptor inhibitors (sunitinib and vatalanib). The activity of bevacizumab has been suggested in small case series and a prospective Phase II trial is ongoing for all grades of recurrent meningioma [17]. Neither the sunitinib or vatalanib trials (VEGF receptor inhibitors) have been reported in a peer-reviewed manuscript; consequently, it is premature to draw conclusions as to the efficacy and, importantly, the associated toxicity of this class of agents, particularly given that these targeted agents are cytostatic and will probably require long-term usage.

How to define activity against meningioma is challenging as the limited literature is inconsistent with respect to outcome end points and predominantly comprised of retrospective studies. There is at present no consensus regarding what constitutes a meaningful response for an antimeningioma agent [1,20–22,24,26,29]. Consequently, various meningioma trials (e.g., imatinib and erlotinib) have reported negatively despite obtaining similar results as another, purportedly positive, study (e.g., Sandostatin LAR) [20–22,24]. These differing interpretations reflect in part differences in prior therapy administered before treatment (e.g., whether surgery and radiotherapy were utilized), differing grades of meningioma and extrapolation from primarily retrospective studies. The only randomized placebo-controlled trial of patients with recurrent grade 1 meningioma in which all patients were previously treated with radiotherapy (SWOG-9005) evaluated the investigational agent RU-486, a progesterone antagonist. A total of 160 subjects were evaluable [27]. Time to progression was similar in both treatment groups suggesting mifepristone was an inactive therapy. The study concluded that a 50% 6-month PFS is a baseline outcome measure from which to compare other medical therapies in similarly treated patients. Importantly, and differing from the SWOG-9005 trial, current management of meningioma has changed as increasingly patients are aggressively treated with multiple modalities of radiotherapy, including both fractionated external beam radiotherapy and stereotactic radiotherapy. In a recent study of HU-treated recurrent surgery- and radiation-refractory WHO grade 1 meningioma (n = 60), 6-month PFS was 10% suggesting a more contemporary baseline with which to compare medical therapies [26]. In a similar study of surgery- and radiation-refractory high-grade meningiomas (n = 35) treated with HU, a 6-month PFS of 3% was seen, suggesting that HU is inactive [29]. It might be argued that this study is representative of the natural history of recurrent surgery- and radiotherapy-refractory high-grade meningioma and consequently serves as a contemporary end point baseline against which to evaluate other agents. Other authors contend that an active agent for recurrent high-grade meningioma is defined by a 6-month PFS of 20–30% [20–23]. These studies demonstrate a need for consensus with respect to definitions of antimeningioma activity, as defined by 6-month PFS, to permit comparisons between studies. Currently, a Response Assessment in Neuro-Oncology (RANO) subcommittee is charged with defining new end points and methods of radiographic assessment in patients with meningioma in the hope of standardizing criteria for response in patients with meningiomas on clinical trials [32].

There are several challenges with respect to treating recurrent meningioma, including the limited understanding of the driver signal pathways relevant to meningioma growth and the consequent lack of defined targets for targeted therapy. Additionally, without a consensus regarding end points such as 6-month PFS, it is difficult to compare trials in recurrent meningioma. There has been a general lack of awareness by the pharmaceutical industry (the most common funding source for brain tumor clinical trials) regarding meningioma and there have been, therefore, no industry-sponsored trials. In

part, this lack of awareness by the pharmaceutical industry is reflected by the limited interest of neuro-oncology cooperative groups, which are predominantly glioma focused. There is also a perception that patients with recurrent meningioma eligible for study are uncommon despite the fact that meningioma constitutes the most frequent primary brain tumor. Lastly, and perhaps correctly, there is a perception by the neuro-oncology community that the systemic treatment of recurrent meningioma following failure of surgery and radiotherapy is futile. These challenges are reflected in the fact that there are very few open prospective trials for patients with recurrent meningioma (and those that exist are all comparatively small, single-arm Phase II studies), which emphasizes an unmet need in neuro-oncology.

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