Medical management of meningioma in the era of precision medicine

Saksham Gupta, BA, Wenya Linda Bi, MD, PhD, and Ian F. Dunn, MD

Center for Skull Base and Pituitary Surgery, Department of Neurosurgery, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts

Surgery is curative for most meningiomas, but a minority of these tumors recur and progress after resection. Initial trials of medical therapies for meningioma utilized nonspecific cytotoxic chemotherapies. The presence of hormone receptors on meningioma ushered in trials of hormone-mimicking agents. While these trials expanded clinical understanding of meningioma, they ultimately had limited efficacy in managing aggressive lesions. Subsequent detection of misregulated proteins and genomic aberrancies motivated the study of therapies targeting specific biological disturbances observed in meningioma. These advances led to trials of targeted kinase inhibitors and immunotherapies, as well as combinations of these agents together with chemotherapies. Prospective trials currently recruiting participants are testing a diverse range of medical therapies for meningioma, and some studies now require the presence of a specific protein alteration or genetic mutation as an inclusion criterion. Increasing understanding of the unique and heterogeneous nature of meningiomas will continue to spur the development of novel medical therapies for the arsenal against aggressive tumors.

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MENINGIOMAS are the most common primary central nervous tumors in adults, comprising more than a third of all brain tumors. Most are WHO grade I, while 15%–20% are considered high grade (WHO grade II or III). While grade I meningiomas largely express an indolent course, high-grade meningiomas are associated with poor prognoses: 10-year overall survival (OS) ranges from 53%–79% for patients with WHO grade II lesions to 14%–34% for those with grade III tumors. Patients with meningioma refractory to conventional surgery or radiation have limited pharmacotherapeutic options.⁷²

Clinical trials for meningioma are challenged not only by a dearth of targets, but also by several qualities of the tumor's growth pattern and epidemiology. First, the relatively indolent nature of WHO grade I meningiomas and the wide variability in the natural history of grade II meningiomas challenge our ability to define consistent outcome measures within a reasonable time frame. The

amount of time necessary to reflect true disease control or progression may exceed that budgeted for a typical clinical trial. Second, the relative efficacy of surgery and adjuvant radiation for meningiomas constrains the burden of progressive meningiomas, especially WHO grade I subtypes, which might be studied in clinical trials. These constraints have frequently prompted the accrual of tumors of different grades and with prior treatments into the same trial to allow sufficient power for the end points, which may then confound the interpretation of results.

Additionally, approaches for measuring meningioma growth vary across studies of tumor progression, with some investigators utilizing maximum diameter; others, maximum area; and still others, three-dimensional volumetric analysis. The lack of consistent clinical end points across studies has limited comparisons between trials and raised calls for standardization of trial techniques.

Medical management of meningioma has continued to

ABBREVIATIONS AKT = alpha serine/threonine-protein kinase; EGFR = epidermal growth factor receptor; OS = overall survival; PDGF = platelet-derived growth factor; PFS = progression-free survival; PFS6 = PFS at 6 months; TGF = tumor growth factor; VEGF = vascular endothelial growth factor.

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evolve in the last 2 decades, mirroring the expansion of therapeutic strategies in human cancers. Studies of non-specific agents have given way to trials that leverage our understanding of specific molecular alterations and the immune environment. These discoveries have motivated trials of novel molecular inhibitors and immunotherapies. In the present review, we summarize the medical management strategies studied for meningioma to date and avenues for future therapeutic development in light of biological insights.

Cytotoxic Chemotherapy

Cytotoxic chemotherapy has generally been reserved for meningiomas refractory to both surgery and radiotherapy (Table 1). A cyclophosphamide, doxorubicin, and vincristine regimen for anaplastic meningioma had modest results despite severe toxicities, with the majority of recipients displaying a stable radiological response and median OS of 5.3 years.⁹ Irinotecan, a topoisomerase I inhibitor, and temozolomide, a DNA alkylator, resulted in 6% and 0% progression-free survival (PFS) at 6 months (PFS6), respectively, for refractory WHO grade I meningioma in phase II trials.^{14,15}

Hydroxyurea, a ribonucleotide reductase inhibitor, offered initial promise in a small case series in which a positive radiographic response was demonstrated in 3 of 4 recurrent meningioma patients who had received the drug.⁶⁴ Further retrospective and prospective studies of hydroxyurea revealed that patients most commonly display a stable response, followed by progressive disease, and that median PFS on hydroxyurea ranges from 2 to 77 months depending on the study population.^{10,13,29,40,48,62,74}

Subsequent clinical trials that assessed the safety and efficacy of combination therapies that included hydroxyurea are discussed further in *Combinatorial Pharmacological Therapies* below.

Hormone-Directed Therapy

Meningioma has been associated with the dysregulation of a number of hormonal axes. Hormone exposure has been implicated in the development of meningioma as evidenced by a female preponderance among patients, tumor growth during pregnancy, and the risk reduction seen in menopause and after oophorectomy.

Tamoxifen, an anti-estrogen agent, did not demonstrate efficacy in two phase II trials, with the majority of patients developing progressive disease.^{23,47} In contrast, the anti-progesterone agent mifepristone was associated with modest positive responses in a minority of patients in several retrospective and prospective single-arm trials.^{25,26} These results motivated a phase III randomized controlled trial assessing the impact of mifepristone on OS and PFS in progressive or recurrent meningioma.³³ While no statistical differences were found between the two treatment arms, the low patient enrollment prevented stratification by tumor grade. Moreover, meningiomas of different grades may differentially express sex hormone receptors and may have obscured potentially salient results from this trial.

Meningiomas demonstrate activation of the growth hormone (GH)/insulin-like growth factor 1 (IGF-1) axis. The

GH/IGF-1 axis is endogenously inhibited by somatostatin, motivating the study of somatostatin analogs in trials. Meningiomas preferentially express somatostatin receptor type 2 (SST2), which can bind the hormone octreotide to decrease cell proliferation.²⁴ Response to octreotide is correlated to high SST and Merlin levels in vitro.²⁴

An initial retrospective analysis on the efficacy of the somatostatin analog octreotide as therapy for 3 refractory meningioma cases suggested its potential to maintain stable disease.¹⁹ Additionally, a retrospective study of octreotide in 8 progressive WHO grade I meningiomas demonstrated 100% PFS at 48 months.⁶⁵ However, other phase II trials that recruited higher proportions of patients with grade II–III meningiomas demonstrated a median PFS ranging from 4 to 5 months.^{34,68}

A phase II trial of pasireotide, another somatostatin analog formulation, showed possible therapeutic benefit in high-grade meningioma.⁵⁵ Notably, patients with high-grade meningioma, all of whom had undergone prior surgery and radiotherapy and most of whom had received chemotherapy, had a median OS of 2.0 years. Radiolabeled [DOTA⁰,Tyr³]-octreotide (DOTATOC) therapy, which targets somatostatin receptors, was tested in a phase II trial and demonstrated stable disease in a majority of progressive meningioma cases and a mean OS of 8.6 years from the initiation of treatment; however, the tumor grade distribution was not reported in this study.⁴⁶

Non-Hormonal Targeted Therapies

The molecular specificity of targeted therapies differentiates them from traditional chemotherapy in providing precise attacks on protein targets. Current therapies act on a range of cellular receptors, signal transduction molecules, cell cycle regulators, and other vital molecules that were initially identified by aberrant protein expression. Targeted therapy for meningioma will necessitate foundational knowledge of these interrelated mechanisms. Antagonists of these pathways have been trialed in meningioma and are discussed below (Table 2).

Vascular Endothelial Growth Factor

Aberrant angiogenesis is a shared characteristic and therapeutic target in many cancers. Vascular endothelial growth factor (VEGF) is a potent activator of angiogenesis with expression levels that correlate with meningioma grade.⁴³ It is also associated with phenotypic characteristics including peritumoral edema and necrosis.^{22,43} Vascular endothelial growth factor signaling further cross-talks with platelet-derived growth factor (PDGF) signaling, another process that has been explored in the treatment of refractory meningiomas, as discussed below.⁴⁵

Targeted anti-angiogenic therapy is a promising avenue for meningioma because of robust pharmaceutical development and VEGF expression in meningioma. In two recent retrospective case series, bevacizumab, a monoclonal antibody against VEGF-A, has shown efficacy in maintaining stable disease in meningiomas refractive to multiple treatment modalities.^{45,52} In one of these studies, bevacizumab led to a median PFS of 17.9 months and PFS6 of 85.7% among 14 patients with WHO grade I–III

TABLE 1. Clinical studies of cytotoxic chemotherapy for meningioma

Authors & Year	Regimen	Mechanism	Study Design	No. of Pts	Prior Op/ RT/ST	WHO Grade*				Best Radiographic Response*						PFS		Median OS
						NA	I	II	III	SD	MR	PR	CR	PD	Median	PFS6		
Schrell et al., 1997	Hydroxyurea	RRI	Retrospective	4	4/3/NA	0	3	0	1	1	1	2	0	0	NA	NA	NA	
Newton et al., 2000	Hydroxyurea	RRI	Retrospective	17	NA	0	16	1	0	11	0	0	0	5	80 wks	NA	NA	
Mason et al., 2002	Hydroxyurea	RRI	Prospective	20	20/8/NA	0	16	3	1	12	1	0	0	7	NA	NA	NA	
Rosenthal et al., 2002	Hydroxyurea	RRI	Retrospective	15	15/1/NA	0	10	5	0	11	0	0	0	4	NA	NA	NA	
Newton et al., 2004	Hydroxyurea	RRI	Prospective	12	12/6/NA	0	8	4	0	3	1	0	0	8	13 mos	NA	NA	
Fuentes et al., 2004	Hydroxyurea	RRI	Prospective	48	28/NA/0	15	18	10	NA	13	0	2	0	21	NA	NA	NA	
Hahn et al., 2005	Hydroxyurea, radiation	RRI	Retrospective	21	23/0/NA	4	13	2	2	19	2	0	0	0	NA	NA	NA	
Weston et al., 2006	Hydroxyurea	RRI	Prospective	6	5/NA/NA	1	5	0	0	3	0	0	0	1	NA	NA	NA	
Chamberlain & Johnston, 2011	Hydroxyurea	RRI	Retrospective	60	60/60/NA	0	60	0	0	21	0	0	0	39	4 mos	10%	NA	
Chamberlain, 2012	Hydroxyurea	RRI	Retrospective	35	35/35/NA	0	0	22	13	15	0	0	0	20	2 mos	3%	NA	
Reardon et al., 2012	Hydroxyurea, imatinib	RRI, PDGFR inhibitor	Phase II	21	7/0/NA	0	8	9	4	NA	NA	NA	NA	NA	7 mos	62%	66 mos	
Kim et al., 2012	Hydroxyurea	RRI	Retrospective	13	13/NA/NA	0	8	5	0	10	0	0	0	3	77 mos	NA	NA	
Karsy et al., 2016	Hydroxyurea, verapamil	RRI	Phase I/II	7	7/5/NA	0	2	5	0	1	0	0	0	6	8 mos	85%	35 mos	
Mazza et al., 2016	Hydroxyurea, imatinib	RRI, PDGFR inhibitor	Phase II	15	15/11/0	0	2	9	1	4	0	0	0	0	4 mos	NA	6 mos	
Chamberlain et al., 2006	Irinotecan	Topoisomerase I inhibitor	Phase II	16	16/16/NA	0	16	0	0	12	0	1	0	3	4.5 mos	6%	7 mos	
Chamberlain et al., 1996	Cyclophosphamide, doxorubicin, vincristine	Combinatory therapy	Phase II	14	14/14/NA	0	0	0	14	12	0	2	0	0	4.6 yrs	NA	5.3 yrs	
Chamberlain et al., 2004	Temozolomide	DNA alkylator	Phase II	16	16/16/NA	0	16	0	0	13	0	0	0	3	5 mos	0%	7 mos	

CR = complete response; MR = minimal response; NA = not available; PD = progressive disease; PDGFR = platelet-derived growth factor receptor; PR = partial response; Pts = patients; RRI = ribosomal reductase inhibitor; RT = radiation therapy; SD = stable disease; ST = systemic therapy.

* Data missing for some cases; therefore, values do not reflect total number of patients for each study.

TABLE 2. Clinical studies of targeted therapy for meningioma

Authors & Year	Regimen	Mechanism	Study Design	No. of Pts	Prior Op/ RT/ST	WHO Grade*				Best Radiographic Response*								PFS		Median OS
						NA	I	II	III	SD	MR	PR	CR	PD	Median	PFS6				
Norden et al., 2009	Erlotinib, gefitinib	EGFR TKI	Phase II	25	25/21/10	0	8	9	8	8	0	0	0	0	17	10 wks	28%	23 mos		
Wen et al., 2009	Imatinib	PDGFR TKI	Phase II	22	22/20/7	0	12	5	5	9	0	0	0	0	10	2 mos	29.4%	NA		
Horak et al., 2012	Imatinib	PDGFR TKI	Retrospective	9	NA	0	1	2	6	7	0	0	0	0	2	16 mos	66.7%	42 mos		
Kaley et al., 2015	Sunitinib	VEGFR + PDGFR TKI	Phase II	36	36/35/NA	0	0	30	6	25	0	1	1	1	8	5.2 mos	42%	25 mos		
Lou et al., 2012	Bevacizumab	Anti-VEGF antibody	Retrospective	14	14/11/9	1	5	5	3	11	0	1	0	2	17.9 mos	86%	NA			
Nayak et al., 2012	Bevacizumab	Anti-VEGF antibody	Retrospective	15	15/15/7	0	0	6	9	13	2	0	0	0	26 wks	43.8%	15 mos			
Nunes et al., 2013	Bevacizumab	Anti-VEGF antibody	Retrospective	15	NA	15	NA	NA	NA	14	0	1	0	0	20 mos	93%	NA			
Alanin et al., 2015	Bevacizumab	Anti-VEGF antibody	Retrospective	7	NA	NA	NA	NA	NA	2	0	5	0	0	NA	NA	NA			
Shih et al., 2016	Bevacizumab, everolimus	Anti-VEGF antibody	Phase II	17	16/12/3	1	4	7	5	15	0	0	0	1	22 mos	69%	23.8 mos			
Raizer et al., 2014	Vatalanib	VEGFR + PDGFR TKI	Phase II	25	25/24/11	1	2	14	8	14	0	1	NA	6	7 mos	60%	26 mos			

TKI = tyrosine kinase inhibitor; VEGFR = VEGF receptor.

* Data missing for some cases; therefore, values do not reflect total number of patients for each study.

meningiomas.⁴⁵ A retrospective review of bevacizumab for *NF2*-associated vestibular schwannomas and meningiomas revealed a radiographic response, defined as at least 20% volumetric shrinkage, in 29% of the meningiomas for a median duration of 3.7 months.⁵⁶ These responses were generally short-lived, however, as median PFS was 15 months.

Platelet-Derived Growth Factor

Models of meningioma highlight the important role of PDGF in tumor development and transformation. Antibodies against PDGF variants inhibit meningioma growth in vitro, and the induction of PDGF β expression in mouse arachnoid is sufficient to generate meningioma.^{58,69} The expression level of certain PDGF and PDGF receptor (PDGFR) subtypes correlates with tumor grade.⁷⁵ The PDGFR inhibitor regorafenib has shown increased survival in in vivo testing using an orthotopic mouse model.⁷⁰ Imatinib mesylate inhibits PDGFR as well as c-Kit and c-Abl, rendering the drug a potential treatment for refractory meningioma. A phase II trial testing imatinib showed modest results, however, with more cases demonstrating radiological progression rather than stable disease.⁷³ A retrospective case series of tumors with positive immunohistological staining for PDGFR demonstrated a median PFS and PFS6 of 16 months and 66.7%, respectively.³²

Sunitinib is a multi-targeted receptor tyrosine kinase inhibitor with activity against the receptors for both VEGF and PDGF and reduces meningioma cell DNA synthesis, viability, and migration in vitro.³ A phase II trial of sunitinib for high-grade meningioma refractory to surgery and radiotherapy yielded a median PFS of 5.2 months and median OS of 25 months.³⁸ Of interest, a case report on sunitinib for a recurrent, rapidly growing WHO grade II skull base meningioma documented a marked reduction of tumor volume that caused cerebrospinal fluid leakage.⁵⁹ Vatalanib is another multi-targeted receptor tyrosine kinase inhibitor that has exhibited modest therapeutic efficacy in a phase II trial for refractory meningioma; grade II cases in the trial had a 7-month median PFS and 26-month median OS.⁶⁰

Epidermal Growth Factor

Epidermal growth factor (EGF) and the EGF receptor (EGFR) represent other therapeutic targets. Higher expression levels are associated with benign meningiomas.⁵¹ A phase II trial of erlotinib or gefitinib, two targeted EGFR inhibitors, for recurrent meningioma demonstrated a median PFS of 10 weeks and PFS6 of 28%.⁶³ The limited efficacy of EGFR inhibitors may be partially explained by differing EGFR expression levels of the trial participants.

Other Pathways

Other pathways involved in cellular growth, cell cycle regulation, transcriptional regulation, and apoptosis have been implicated in meningioma tumorigenesis and growth. Tumor growth factor (TGF) α expression is associated with recurrence and is negatively associated with survival.⁴⁴ Expression of TGF β increases activity of the SMAD signaling pathway.³⁵ In addition, the expression of

TGF β receptor III is associated with higher-grade meningioma.³⁶

Cyclins and cyclin-dependent kinases (CDKs) regulate cell cycle progression and contribute to the hallmark overproliferation associated with cancer. Cyclin D1 expression is associated with an increased tumor grade and recurrence in meningioma.¹⁶ A screen for compounds to identify in vitro tumor growth inhibitors identified silvestrol as an inhibitor that putatively acts through cyclin downregulation that induces G2/M cell cycle arrest.⁵⁷

Histone deacetylase (HDAC) inhibitors exert cytostatic effects on replicating cells by hyper-acetylating DNA. The HDAC inhibitor AR-42 induces meningioma apoptosis in vitro.⁸ It has also caused tumor regression in a xenograft mouse model of meningioma.⁸ A truncated form of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) that cannot initiate apoptotic signaling is correlated with meningioma grade.⁴²

Molecularly Targeted Therapies From Genomic Analyses

Next-generation sequencing technology has yielded insights into potential oncogenic drivers of meningioma. Identified mutations include *AKT1*, *SMO*, *KLF4*, *TRAF7*, *PIK3CA*, *SUFU*, *BAP1*, *SMARCB1/E*, *POL2RA*, and others, in addition to the well-characterized *NF2*.^{1,7,17,66} Screening tumors prior to adjuvant therapy may improve the tailoring of individual regimens and trial stratification. *BAP1* mutations highlight additional benefits of genomic screening, including those for possible syndromic patients.

PI3K/AKT/mTOR Pathway

The phosphoinositol-3 kinase (PI3K) pathway transduces growth factor signals and is upregulated in many cancers. Activation of PI3K leads to the phosphorylation and activation of alpha serine/threonine-protein kinase (AKT), which directly activates mammalian target of rapamycin (mTOR). *AKT1* and *PIK3CA* mutations were identified in 9% and 7% of meningiomas, respectively, which are largely WHO grade I tumors.^{1,28,50} *AKT1*-mutant meningiomas demonstrate a proclivity for the anterior fossa skull base (19%).

AKT1 mutations, observed nearly exclusively in non-*NF2* altered tumors, have generated particular excitement due to the presence of inhibitors currently in clinical trial. A case of metastatic, highly refractory meningioma that demonstrated ex vivo AKT inhibitor sensitivity had stable disease up to 1 year after initiating AKT inhibitor therapy with AZD5363.⁷¹ The role of AKT1 inhibition in the treatment of recurrent or progressive meningioma is currently in clinical trial (see below).

SMO

Mutations in *SMO* have been detected in about 6% of non-*NF2* altered meningiomas, with the majority of *SMO*-altered tumors found at the skull base, particularly at the olfactory groove.^{6,17} Up to 28% of olfactory groove meningiomas harbor *SMO* mutations, and this molecular signature may also portend a poorer prognosis among WHO

grade I olfactory groove tumors.⁶ A phase II trial is underway to explore the efficacy of SMO inhibition in recurrent or progressive meningioma.

BAP1

Breast cancer type 1 susceptibility protein (BRCA1)-associated protein-1 (BAP1) is a tumor suppressor that acts via deubiquitinase activity on nucleosomes, and *BAP1* inactivating mutations have been identified in meningiomas with rhabdoid morphology.⁶⁶ *BAP1*-mutant meningiomas have been found to be at least WHO grade II and clinically aggressive. The presence of *BAP1* mutations confers an elevated risk for multiple types of cancer, so knowledge of their expression could modify an individual's tumor screening and surveillance. Enhancer of zeste homolog 2 (EZH2) inhibitors and their homologs have demonstrated in vitro inhibition of BAP1-mutant mesotheliomas, which have elevated EZH2 mRNA levels. The EZH2 inhibitor tazemetostat is currently undergoing clinical trial in BAP1-deficient relapsed or refractory malignant mesothelioma (NCT02860286, <http://www.clinicaltrials.gov>). Enhancer of zeste homolog 2 is similarly upregulated in high-grade meningioma and may present an opportunity for targeted inhibition.³¹

Immunotherapy

Immunotherapy in refractory meningioma dates to initial experiences with interferon (IFN)- α after it was shown to reduce meningioma growth by 70%–100% in vitro.⁴¹ A phase II pilot study testing IFN- α on 6 recurrent meningioma cases showed a positive response to treatment with stable disease or a slight regression.³⁷ Another phase II trial on 35 WHO grade I meningiomas refractory to surgery, radiation, and chemotherapy demonstrated a favorable median PFS of 7 months and PFS6 of 54%.¹² A similar trial on high-grade meningiomas demonstrated a median PFS of only 3 months and PFS6 of 17%.¹¹

Despite these initially grim results, several lines of evidence support a role for immunotherapy in meningioma.⁵ First, these tumors recruit immune populations, especially monocytes and cytotoxic T cells, with higher concentrations of macrophages in higher-grade tumors.²⁷ Second, half of the mutations found in meningioma are predicted to be neo-antigenic with a higher number observed in high-grade tumors.⁴ Third, meningiomas exist outside the blood-brain barrier and may be modulated by the systemic immune response. Fourth, and most salient for therapeutics, high-grade meningiomas with higher expressions of the immune checkpoint markers programmed cell death protein 1 (PD-1) and PD-1 ligand (PD-L1) are associated with worse survival, independent of tumor grade, extent of resection, and prior recurrence.³⁰ Programmed cell death protein 1 is a cell surface receptor on T cells and binds PD-L1 on antigen-presenting cells and tumors cells to inhibit T-cell activation. Antibodies directed against the PD-1/PD-L1 axis strengthen the immune response and have achieved objective responses in several cancers. Anaplastic meningioma cells highly express PD-L1, suggesting that anti-PD-1/PD-L1 inhibitors may offer clinical efficacy for these tumors.

TABLE 3. Active, enrolling trials of medical therapies for meningioma registered on clinicaltrials.gov

Official Study Title	Drug	Phase	No. of Participants	Sponsor	Completion Date	Trial Registration No.
Exploratory Evaluation of AR-42 Histone Deacetylase Inhibitor in the Treatment of Vestibular Schwannoma and Meningioma	AR-42	0	20	Massachusetts Eye and Ear Infirmary, Johns Hopkins University, Mayo Clinic, Stanford University, Ohio State University, Nationwide Children's Hospital	August 2018	NCT02282917
Combination of Everolimus and Octreotide LAR in Aggressive Recurrent Meningiomas	Everolimus, octreotide	II	20	Assistance Publique Hopitaux de Marseille	January 2018	NCT02333565
Ribociclib (LEE011) in Preoperative Glioma and Meningioma Patients	Ribociclib	0/II	48	St. Joseph's Hospital and Medical Center	December 2018	NCT02933736
A Study of Nivolumab in Adult Participants With Recurrent High-Grade Meningioma	Nivolumab	II	25	Dana-Farber Cancer Institute	August 2018	NCT02648997
Vismodegib and FAK Inhibitor GSK2256098 in Treating Patients With Progressive Meningiomas	Vismodegib, GSK2256098	II	69	Alliance for Clinical Trials in Oncology, National Cancer Institute, GlaxoSmith-Kline, Genentech Inc., Brain Science Foundation	August 2019	NCT02523014
Phase II Trial of Pembrolizumab in Recurrent or Residual High Grade Meningioma	Pembrolizumab	II	26	Massachusetts General Hospital, Merck Sharp & Dohme Corp.	March 2021	NCT03279692
Trial of Selumetinib in Patients With Neurofibromatosis Type II Related Tumors (SEL-TH-1601)	Selumetinib	II	34	Children's Hospital Medical Center, AstraZeneca	May 2020	NCT03095248
Immune Checkpoint Inhibitor Nivolumab in People With Select Rare CNS Cancers	Nivolumab	II	180	National Cancer Institute	December 2021	NCT03173950

A report of the PD-1 inhibitor nivolumab for lung cancer in a patient with concurrent meningioma demonstrated a 24% radiographic volume reduction in the meningioma.²⁰ Trials of nivolumab (NCT03173950, <http://www.clinicaltrials.gov>) and another PD-1 inhibitor, pembrolizumab (NCT03279692, <http://www.clinicaltrials.gov>), for meningioma are currently recruiting participants.

Combinatorial Pharmacological Therapies

Targeted therapies have great potential in personalized medicine by allowing each patient's mutagenic profile to guide their treatment. An inherent limitation to this paradigm is the "one mutation, one drug" assumption. Intratumoral genomic heterogeneity renders subpopulations of tumor cells immune to therapies targeted to alterations found in neighboring cell populations, resulting in the subsequent outgrowth of these resistant clones. Combinatorial therapies mitigate this problem by targeting multiple pathways simultaneously. The intratumoral genomic heterogeneity observed in recurrent meningioma underlies the need for therapeutic approaches that efficaciously target different subpopulations.

Authors of recent studies have examined the safety and efficacy of combinatorial therapy in meningioma with promising results. In a phase II trial of hydroxyurea and imatinib for patients with progressive or recurrent meningioma, the majority of cases demonstrated stable disease,

though no cases showed a positive radiological response.⁶¹ The combination was well tolerated and PFS6 for all cases was 61.9%. A randomized phase II trial testing the same combinatorial therapy was prematurely concluded because of slow enrollment, although all patients who enrolled demonstrated stable disease.⁴⁹ A phase I/II trial of hydroxyurea and verapamil, a calcium-channel antagonist that enhances hydroxyurea's cytostatic effect in *in vitro* and *in vivo* models of meningioma, demonstrated side effects in 86% of patients and a median PFS and PFS6 of 8 months and 85%, respectively, in refractory meningioma.²¹

Current Trials

Currently, there are 8 active, enrolling trials assessing novel medical strategies for meningioma, focusing on cytotoxic chemotherapy, targeted therapy, combinatorial therapy, and immunotherapy (Table 3). These include phase 0 trials of AR-42 (NCT02282917) and the mTOR inhibitor everolimus (NCT01880749, not recruiting). AR-42 will gauge the efficacy of epigenomic manipulation in meningioma treatment, while everolimus will target the mTOR pathway, which has been shown to be overactive in some meningiomas. Currently enrolling phase II trials include the cyclin/CDK inhibitor ribociclib (NCT02933736); the hedgehog pathway inhibitor vismodegib and the focal adhesion kinase inhibitor GSK2256098 (NCT02523014); the MEK1 inhibitor selumetinib (NCT03095248); the PD-1

inhibitors nivolumab (NCT03173950) and pembrolizumab (NCT03279692); and a combinatorial regimen consisting of everolimus and octreotide (NCT02333565, status unknown).

Prior trials have demonstrated that no individual agent or class of agents is likely to produce a favorable response in all recurrent and progressive meningiomas. Rather, different therapeutics will probably be more efficacious for certain tumors depending on the genomic makeup of the tumor and the local immune microenvironment among other factors. The enrolling trials on ribociclib, vismodegib, and selumetinib incorporate genomic data for inclusion criteria, which may provide guidance in predicting biological subsets of meningiomas that will respond favorably.

Future Directions

Expanding knowledge of meningioma biology is powering the development of novel therapeutics to challenge this disease. Genomics and epigenetic signatures may also improve prognostication and trial stratification. Evolving quantitative radiomic characterizations of meningioma may provide additional tumor stratification tools and upfront prediction of tumor behavior on initial diagnosis. Finally, acknowledging the cellular heterogeneity of meningioma conferred by cancer stem cells provides a parallel avenue for therapeutic discoveries in multidrug-resistant meningioma.

Conclusions

Few options exist to medically manage refractory and progressive cases of meningioma. Advances in molecular biology and genomics have led to the development of novel molecular inhibitors that can target aberrantly expressed oncogenic and immunomodulatory molecules. Emerging trials for meningioma are beginning to integrate genomic inclusion criteria, with hope to refine future clinical outcomes within the precision medicine paradigm.

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Disclosures

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Author Contributions

Conception and design: all authors. Acquisition of data: all authors. Analysis and interpretation of data: all authors. Drafting the article: all authors. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Dunn. Administrative/technical/material support: all authors. Study supervision: all authors.

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Correspondence

Ian F. Dunn: Brigham and Women's Hospital, Boston, MA. idunn@partners.org.