Targeted drug therapy for meningiomas

ANDREW D. NORDEN, M.D., JAN DRAPPATZ, M.D., AND PATRICK Y. WEN, M.D.

Division of Neuro-Oncology, Department of Neurology, Brigham and Women's Hospital; and Center for Neuro-Oncology, Dana-Farber-Brigham and Women's Cancer Center, Boston, Massachusetts

✓ Although advances in surgery, radiation therapy, and stereotactic radiosurgery have significantly improved the treatment of meningiomas, there remains an important subset of patients whose tumors are refractory to conventional therapy. Treatment with traditional chemotherapeutic agents has provided minimal benefit. In this review, the role of targeted molecular therapies for recurrent or progressive meningiomas is discussed. (DOI: 10.3171/FOC-07/10/E12)

KEY WORDS • kinase inhibition • meningioma • targeted drug therapy

MENINGIOMAS are primary central nervous system tumors composed of neoplastic meningeothelial (arachnoid cap) cells.⁶⁸ They represent the most common type of benign intracranial tumor. With an annual incidence of approximately 2.3 to 6 per 100,000 persons, meningiomas account for approximately 13 to 26% of primary brain tumors in adults.^{7,26,74,135} Many meningiomas are asymptomatic in life and are found incidentally in 1.4% of autopsies.⁷⁴ They occur twice as often in women as in men, and the mean age of patients at diagnosis is approximately 58 years.^{7,26} Ninety percent of meningiomas are intracranial, and of these 90% are supratentorial. Meningioma risk factors that account for a relatively small number of cases include NF2 and cranial irradiation.^{26,74,105,135}

The WHO classifies this tumor into three main categories: benign (WHO Grade I), atypical (WHO Grade II), and malignant (anaplastic) (WHO Grade III), based on the degree of anaplasia, number of mitoses, and presence of

necrosis.⁷⁴ Over 90% of meningiomas are histologically benign, and these lesions are associated with a low rate of recurrence (7–20%).^{68,74,105} Atypical lesions are much less common. They account for 4.7 to 7.2% of meningiomas and are associated with a 40% recurrence rate despite resection.¹⁰⁵ Malignant meningiomas represent only 1 to 2.8% of meningiomas but recur in 50 to 80% of cases and usually result in death within 2 years of diagnosis.^{68,74}

Molecular Pathogenesis of Meningiomas

There has been some progress in understanding the molecular genetics of meningiomas,^{68,105,119} but compared with our knowledge of gliomas, relatively little is known.¹³⁵ Meningiomas constitute one of the first types of solid tumors to be associated with a characteristic cytogenetic change, loss of heterozygosity of chromosome 22.^{68,105,141} The *NF2* gene is the primary target, with mutation or deletion constituting an early event in half of sporadic and most NF2-associated meningiomas.^{46,68,105} The *NF2* gene encodes a protein, termed merlin or schwannomin, that regulates cell growth and motility by linking the cytoskeleton to cell membrane proteins.^{68,105} Interestingly, the likelihood of *NF2* mutation appears to vary with histological subtype. In a recent study,⁴⁶ 126 sporadic meningioma specimens were analyzed with microarray-based comparative genomic hybridization. The frequency of biallelic *NF2* inactivation was 52% in fibroblastic tumors compared with 18% in meningeothelial tumors, both of which are benign meningioma subtypes; this finding suggests that *NF2* inactivation may not be a critical step in the pathogenesis of meningeothelial meningiomas. Fifty-one tumors (40%) showed no evidence of loss of the long arm of chromosome 22 (22q), and 16 (13%) showed partial 22q loss that did not involve the *NF2* locus. These findings indicate that additional genes on 22q

Abbreviations used in this paper: AED = antiepileptic drug; CDK = cyclin-dependent kinase; CML = chronic myelocytic leukemia; EGF = epidermal growth factor; EGFR = EGF receptor; ET = endothelin; GF = transforming growth factor; GH = growth hormone; GHR = GH receptor; HGF/SF = hepatocyte growth factor/scatter factor; HSP90 = heat shock protein 90; IAP = inhibitors of apoptosis proteins; IGF = insulin-like growth factor; IGFBP = IGF binding protein; IGFR = IGF receptor; MAPK = mitogen-activated protein kinase; MEK = MAPK kinase; mTOR = mammalian target of rapamycin; NABTC = North American Brain Tumor Consortium; NF2 = neurofibromatosis type 2; PDGF = platelet-derived growth factor; PDGFR = PDGF receptor; PI3K = phosphatidylinositol-3-kinase; PKC = protein kinase C; TFPI-2 = tissue factor pathway inhibitor 2; TPLC = phospholipase C; TRAIL = tumor necrosis factor-related apoptosis-inducing ligand; VEGF = vascular endothelial growth factor; VEGFR = VEGF receptor; WHO = World Health Organization.

and elsewhere in the genome have an important pathogenic role in the development of a subset of meningiomas. Candidate genes on 22q include *BCR*, implicated in CML; *Rgr*, an oncogene involved in Ras signaling; and the zinc finger protein-encoding gene *ZCWC1*.⁴⁶ Like merlin, the product of the *DAL-1* gene (*DAL-1* or Protein 4.1B) may play an important role early in meningioma tumorigenesis.^{68,104,105} Recurrent meningiomas often are characterized by loss of 14q.¹⁰⁵ Transition to atypical meningiomas is associated with losses on 1p, 6q, 10q, 14q, 18q, and gains on 1q, 9q, 12q, 15q, 17q, and 20q, together with increased telomerase activity and loss of progesterone receptor expression.^{68,105,135} Malignant meningiomas are associated with gains on 17q, losses on 9p (*CDKN2A/B*, *p14ARF*), and further losses on 1p, 6q, 14q, and 18q, as well as loss of progesterone receptor expression.^{68,105,135}

The results of gene expression profiling studies have distinguished benign meningiomas from atypical and malignant tumors and confirmed previously noted altered expression of GHR, IGFBP-7, endothelin receptor A (ET-A), and IGF-2.¹²⁹ Additional genes were noted to be differentially overexpressed, including genes that encode cathepsin K (cellular protease associated with an invasive tumor phenotype), midkine (mitogenic and angiogenic factor), and ear-2 (nuclear orphan receptor associated with hormonal gene regulation). Other genes such as *Rad* (nm23 metastasis suppressor), *BCR*, and *junB* (represses cyclin D and cell proliferation) proved to be downregulated in high-grade meningiomas.¹²⁹ More recent microarray studies showed that losses on chromosomes 10 and 14 in high-grade meningiomas were associated with distinct expression profiles including increased expression of several genes related to the IGF (*IGF-2*, *IGFBP3*, and *AKT3*) or wingless (WNT; *CTNNB1*, *CDK5R1*, *ENC1*, and *CCND1*) pathways.¹³⁸ Proteomic analysis may also help to elucidate the molecular events that underlie the transition from benign to atypical or malignant meningiomas.¹⁰¹

In this review, the treatment of meningiomas with targeted molecular therapies will be discussed.

Current Therapies for Meningiomas

Current therapies for meningiomas involve surgery, radiation therapy, and stereotactic radiosurgery.^{15,16,24,30,40,87,89,110,135} For the majority of patients with benign meningiomas and a subset of patients with atypical meningiomas, these therapies are effective in achieving tumor control. There is, however, an important group of patients with inoperable or higher-grade tumors in whom disease recurs following surgery and radiation therapy. The treatment options for these patients are currently inadequate.

To date chemotherapy has had only a very limited role in the treatment of meningiomas. Data from small clinical trials and case series suggest that most chemotherapeutic agents have minimal activity against meningiomas.^{14,16,66,87} The evaluation of chemotherapy has also been complicated by the lack of data regarding the natural history of untreated meningiomas. Many chemotherapy studies have demonstrated variable periods of disease stabilization, but it is difficult to know whether this represents an improvement because benign meningiomas grow slowly and may appear radiographically stable for prolonged periods.^{49,142}

In general, chemotherapeutic agents (such as dacarbazine and adriamycin) that have activity in other soft tissue tumors have produced disappointing results in patients with meningiomas.¹⁶ Hydroxyurea, an oral ribonucleotide reductase inhibitor, arrests meningioma cell growth in the S phase of the cell cycle and induces apoptosis.¹²² In a preliminary report, hydroxyurea (1000–1500 mg/day; 20 mg/kg/day) decreased tumor size in three patients with recurrent benign meningiomas and prevented recurrent disease for 24 months in a patient with a completely resected malignant meningioma.¹²³ Several more recent studies suggest that hydroxyurea has modest activity; responses are uncommon but some patients appear to experience disease stabilization.^{23,75,80,96,114} The Southwest Oncology Group conducted a Phase II study to further evaluate the role of hydroxyurea in meningiomas (SWOG-S9811). This study is closed to accrual, but the final results are not yet available.

There have been reports of small numbers of patients with malignant meningiomas who responded to recombinant interferon α -2b.^{60,90} Temozolomide (Temodar, Schering-Plough; TMZ), an alkylating agent with activity in malignant gliomas, was evaluated in 16 patients with refractory meningiomas and showed negligible activity.¹⁸ The topoisomerase inhibitor irinotecan (Camptosar, Pfizer; CPT-11) caused moderate toxicity in 16 patients with benign meningiomas and had no demonstrable activity.¹⁷ A large number of cytotoxic agents are under evaluation for sarcomas and other systemic malignancies.⁸⁸ Most of these have not been evaluated in meningiomas, and it is possible that some may have modest activity. However, it is likely that the more novel therapeutic approaches discussed below will provide a greater chance of improving the outcome for patients with meningiomas.

Challenges in the Development of Effective Therapies for Meningiomas

In contrast to the extensive understanding of the molecular pathogenesis and biology of systemic malignancies, and even brain tumors such as malignant gliomas, relatively little is known about the molecular pathogenesis of meningiomas and the critical molecular changes driving tumor growth.^{54,68,105,119} Overexpression of various growth factors—including PDGF, EGF, and VEGF—and their receptors, and signal transduction pathways—such as the Ras/MAPK, PI3K-Akt, and PLC- γ 1-PKC pathways—have been implicated, but their relative significance is largely unknown.^{54,119} As a result, the most important molecular targets may remain to be elucidated.

Another factor limiting progress in the development of more effective therapies for meningiomas is the lack of robust cell lines and animal models. There is a need for animal models that replicate the genetic changes in meningiomas with a high frequency of spontaneous meningioma development, benign meningioma lines for in vitro and in vivo studies, and meningeal-specific promoters. Many of the existing meningioma cell lines are derived from malignant meningiomas and probably contain culture-induced artifacts and lack progesterone receptors.¹⁰⁵ There are some orthotopic^{11,85} and genetic models⁶¹ in development that appear promising. Recently, two cell lines were developed from benign meningioma specimens via immortalization with

human telomerase reverse transcriptase and SV40 large T antigen. Orthotopic tumors with immunostaining patterns similar to those of human meningiomas were established from both cell lines in athymic nude mice.¹¹ Another model uses a Cre recombinase technology to inactivate *NF2* in arachnoid cells, resulting in intracranial meningotheelial hyperplasia and meningiomas in 30% of mice.⁶¹ These models may aid in the preclinical evaluation of novel therapies.

The lack of data regarding the natural history of untreated meningiomas is another important limiting factor that impedes progress. Without such data it is difficult to know if the periods of disease stabilization reported in various studies represent an improvement over no therapy.

A final factor limiting progress is the relatively small number of patients with meningiomas who require additional therapies after treatment with surgery and radiation therapy. In general, there is little incentive for pharmaceutical companies to evaluate their therapies in meningiomas because of the small potential market. It is hoped that, as the molecular pathogenesis of these tumors becomes better understood, a compelling case can be made for evaluating specific agents directed at critical molecular targets.

In the next section, targeted molecular drugs that have a potential role against meningiomas will be reviewed in detail. These therapies have been discussed in other recent reviews.^{54,87,110,131}

Molecular Targets and Related Agents

Recently, it has become apparent that many human diseases result from aberrations in cell signaling pathways. Protein tyrosine kinases play a fundamental role in signal transduction, and deregulated activity of these enzymes has been observed in many cancers. Therefore, specific inhibitors of tyrosine kinases could have therapeutic applications in the treatment of cancer, with potentially lower toxicity and/or higher, prolonged response rates.^{2,31} The prototypical targeted molecular agent is imatinib mesylate (Gleevec, Novartis), which has shown significant benefit in CML²⁹ and gastrointestinal stromal tumors.²⁵ There is also a growing experience with targeted molecular agents in malignant gliomas.^{19,62,132} To date, however, there have been minimal data on the use of these agents in meningiomas.

In contrast to the extensive work on understanding the genetics of meningiomas, relatively little work has been conducted in understanding the growth factors, their receptors, and the signal transduction pathways that are critical to meningioma growth.^{54,87,110} Platelet-derived growth factor, EGF, VEGF, IGF, TGF- β , and their receptor tyrosine kinases, together with their downstream signaling pathways including the Ras/MAPK pathway, the PI3K/Akt pathway, the PLC- γ 1-PKC pathway, and the TGF- β -SMAD pathways, are all thought to be important in meningioma growth (Fig. 1).⁵⁴

Platelet-Derived Growth Factor Receptors

Platelet-derived growth factor is a fundamental driver of cell proliferation in normal development and in a variety of pathological conditions, including cancer.¹⁰⁶ Accumulating evidence suggests that PDGF plays an important role in meningioma growth.^{6,82,92,128,139} Most meningiomas of all

histological grades express PDGF ligands AA and BB and the PDGF- β receptor.^{6,82,92,128,139} Expression levels may be higher in atypical and malignant meningiomas than in benign meningiomas.¹³⁹ Laboratory data suggest that an autocrine PDGF loop supports meningioma cell growth and maintenance.⁸² When PDGF-BB is applied to cultured meningioma cells, MAPK⁵⁸ and c-fos⁶³ are activated and tumor cell proliferation is enhanced. Conversely, anti-PDGF-BB antibodies inhibit cell growth.¹²⁷ These data provide a sound rationale for testing PDGF inhibitors in meningioma patients.

Imatinib is a potent inhibitor of the Bcr-Abl, PDGF- α and PDGF- β receptors, and c-Kit tyrosine kinases.¹⁰ Its ability to inhibit PDGFR with an IC₅₀ of 0.1 μ M suggests that it may have therapeutic potential in meningiomas. The NABTC conducted a Phase II study of imatinib in patients with recurrent meningiomas (NABTC 01-08).¹³⁴ Patients were stratified into two cohorts: 1) those with benign meningiomas, and 2) those with atypical and malignant meningiomas. As imatinib is metabolized by the cytochrome P450 system (3A4), patients could not be receiving enzyme-inducing AEDs. Patients initially received 600 mg/day of imatinib; the dose was increased in the second cycle to 800 mg/day if no significant toxicity was observed in the first cycle. Twenty-three patients were enrolled into the study (13 with meningiomas, five with atypical meningiomas, and five with malignant meningiomas). Although the treatment was generally well tolerated, imatinib had minimal activity. Of the 19 patients in whom response could be evaluated, 10 had experienced disease progression at the first scan; in the other nine the disease was stable. There were no radiographic responses. Overall median duration of progression-free survival was 2 months (range 0.7–18 months); the 6-month progression-free survival rate was 29.4%. For benign meningiomas, median duration of progression-free survival was 3 months and the 6-month rate was 45%. For the atypical and malignant meningiomas, median progression-free survival was 2 months and the 6-month rate was 0%. Several other inhibitors of PDGF are undergoing evaluation, including sunitinib, MLN518, dasatinib, AMN 107, pazopanib, sorafenib, CP673451, and CHIR 265. Some of these, such as MLN518, are more potent PDGFR inhibitors than imatinib, whereas others target additional kinases that are potentially important in meningiomas. For example, sunitinib and pazopanib also inhibit VEGFR 1, 2, and 3 as well as c-Kit, while sorafenib and CHIR 265 inhibit VEGFR, c-Kit and Raf. These drugs may be more effective than imatinib as monotherapy against meningiomas.

There is also interest in combining imatinib with hydroxyurea, the cytotoxic chemotherapy agent with the most activity in meningiomas. Although a recent Phase I/II trial of imatinib as monotherapy for recurrent malignant glioma showed minimal activity,¹³³ encouraging results have been reported for a study in which 33 patients with recurrent glioblastoma multiforme were treated with both imatinib mesylate (400 mg/day or 500 mg twice/day, depending on concurrent use of enzyme-inducing AEDs) and hydroxyurea (500 mg twice/day).¹¹² After a median follow up of 58 weeks, a complete response was achieved in one case, a partial response in two cases, and the disease was stable in 14 cases. The 6-month progression-free survival rate was 27%.

FIG. 1. Selected signaling pathways in meningiomas and molecular targets for drug therapy. ERK = extracellular signal-regulated kinase; FT = farnesyltransferase; HDAC = histone deacetylase; PDK1 = 3-phosphoinositide-dependent protein kinase 1; PIP2 = phosphatidylinositol (4, 5)-bisphosphate; PIP3 = phosphatidylinositol (3, 4, 5)-trisphosphate; PTEN = phosphatase and tensin homologue deleted on chromosome 10. Adapted from: *Expert Rev Anticancer Ther* 6:733–754, 2006, with permission of Future Drugs Ltd.

Epidermal Growth Factor Receptor

The EGFR is overexpressed in more than 60% of meningiomas.^{3,12,55,59,72,118,130} Both EGF and TGF- α activate these receptors and stimulate meningioma growth in vitro,^{54,55,130} supporting the concept that activation of EGFRs in human meningiomas by autocrine/paracrine stimulation may contribute to the proliferation of these lesions. Increased TGF- α immunoreactivity in meningiomas has been associated with aggressive growth.^{51,54,72}

The NABTC conducted two trials of EGFR inhibitors in the treatment of meningiomas. In NABTC 01-03, patients with recurrent or progressive meningiomas who were not being treated with enzyme-inducing AEDs were treated with 150 mg/day of erlotinib (Tarceva, Genentech). In NABTC 00-01, patients with recurrent or progressive meningiomas who were not being treated with enzyme-inducing AEDs were treated with 500 mg/day of gefitinib (Iressa, Astra-Zeneca). In both studies, the drugs were reasonably well

tolerated; the main signs of toxicity were the expected adverse effects of rash and diarrhea. Both studies have been closed to accrual, but the final results are not yet available.

In addition to gefitinib and erlotinib, a large number of other agents are currently undergoing evaluation for the treatment of other tumors. These inhibit EGFR alone or together with other receptor tyrosine kinases that may have therapeutic potential in meningiomas (Table 1). For example, lapatinib inhibits EGFR and HER2, HKI-272 inhibits all subtypes of the EGFR, and ZD6474 (Zactima, Astra-Zeneca) inhibits EGFR and VEGFR.

Although EGFR monoclonal antibodies have been effective for some systemic malignancies (for example, cetuximab in colorectal cancer), they have generally not been used for brain tumors because of concern regarding the ability of these agents to pass through the blood–brain barrier in sufficient concentrations to produce a therapeutic effect. Since the blood–brain barrier is not a factor in most meningiomas, it is possible that these antibodies may be

TABLE 1

*Selected potential targeted molecular therapies for the treatment of meningiomas**

Apoptosis Enhancers ABT737 (Bcl-2 inhibitor) AT101 (Bcl-2 inhibitor) fenretinide (multiple targets) GX15-070 (Bcl-2 inhibitor) αVβ3 and αVβ5 Integrin Inhibitor cilengitide Cell-Cycle Inhibitors AG024322 (pan-CDK inhibitor) AZ703 (CDK 2, 1 inhibitor) BMS-387032 (CDK 2, 1 inhibitor) CINK4 (CDK 4, 6 inhibitor) E7070† flavopiridol (pan-CDK inhibitor) PD-0332991 (CDK 4, 6 inhibitor) seliciclib (CDK 2, 1 inhibitor) c-MET (HGF/SF) Inhibitors AMG-102 XL880 (VEGFR2, PDGFR, c-Kit, Tie-2 inhibitor) EGFR Inhibitors AEE788 (VEGFR inhibitor) BIBW 2992 (HER2 inhibitor) cetuximab (Erbix) EMD 72000 erlotinib (OSI-774, Tarceva) gefitinib (ZD1839, Iressa) HKI-272 (pan-EGFR inhibitor) lapatinib (GW-572016; ErbB2 inhibitor) mAb 806 nimotuzumab (TheraCIM) panitumumab (Vectibix) ZD6474 (Zactima; VEGFR inhibitor) Endothelin-A Inhibitors astrasentan (Xinlay) ZD4054 Farnesyltransferase Inhibitors lonafarnib (SCH 66336, Sarasar) tipifarnib (R115777, Zarnestra) Histone Deacetylase Inhibitors depsipeptide vorinostat (SAHA) valproic acid HSP90 Inhibitors 17AAG 17DMAG IPI504 MEK Inhibitors AZD6244 PD0325901	mTOR Inhibitors AP23573 everolimus (RAD001) rapamycin temsirolimus (CCI-779) PDGFR Inhibitors AMN 107 (c-Kit, Bcr-Abl inhibitor) CHIR 265 (Raf, VEGFR, c-Kit inhibitor) CP-673-451 dasatinib (Src, c-Kit, ephrin A inhibitor) imatinib mesylate (Gleevec) MLN518 (c-Kit inhibitor) pazopanib (GW786034; VEGFR, c-Kit inhibitor) sunitinib (Sutent; VEGFR, c-Kit inhibitor) vatalanib (PTK787; VEGFR inhibitor) XL-999 (VEGFR, FGFR inhibitor) PKC β2 Inhibitor enzastaurin (LY31761) PI3K Inhibitor BEZ235 Proteasome Inhibitor bortezomib (Velcade) Raf Kinase Inhibitor sorafenib (Nexavar, BAY 43-9006; VEGFR, PDGFR inhibitor) Src Inhibitors AZD0530 dasatinib TGF-β/TGF-β Receptor Inhibitors AP12009 GC1008 SB-431542 VEGF Inhibitors bevacizumab (Avastin) VEGF trap VEGFR Inhibitors AEE788 (EGFR inhibitor) AG013736 AMG 706 AZD2171 CEP-7055 CHIR 265 (Raf, PDGFR, c-Kit inhibitor) CHIR-258 (PDGFR, FGFR, c-Kit, FLT-3 inhibitor) GW786034 (c-Kit inhibitor) sorafenib (Nexavar, BAY 43-9006; Raf kinase, PDGFR inhibitor) sunitinib (Sutent; PDGFR, c-Kit inhibitor) vatalanib (PTK787; PDGFR inhibitor) XL-999 (PDGFR, FGFR inhibitor) ZD6474 (Zactima; EGFR inhibitor)
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* Additional names and mechanisms of action are given in parentheses. Proprietary information for therapeutic agents discussed is given at the first mention in the text except for the following, which are only mentioned in this table: Erbitux (Bristol-Myers Squibb and ImClone Systems), TheraCIM (YM BioSciences), Vectibix (Amgen), Velcade (Millenium). Abbreviations: FGFR = fibroblast growth factor receptor; SAHA = suberoylanilide hydroxamic acid; TGF β R = TGF- β receptor.

† The mechanism by which this agent inhibits the cell cycle is unknown.

effective in these tumors. To date very few studies have evaluated the therapeutic potential of these agents in meningiomas. In a Phase I study of a murine monoclonal antibody against EGFR in nine patients with either gliomas or meningiomas, treatment was reasonably well tolerated. No radiographic responses were detected, but efficacy data are difficult to interpret in a study involving so few patients.²¹ Currently, several anti-EGFR antibodies—including cetuximab, panitumumab, EMD 72000, nimotuzumab, and mAb 806—are under evaluation for other malignancies. Trials of these agents in meningiomas may be worthwhile, especially if combined with correlative studies examining whether the antibodies can achieve therapeutic concentrations in meningiomas and inhibit EGFR in vivo.

The MAPK Pathway

Signal transduction from activated tyrosine kinases such

as EGFR and PDGFR is mediated in part by the Ras/Raf/MAPK pathway and the PI3K/Akt pathways. Meningioma growth is stimulated in vitro by PDGF-BB via the MAPK pathway, which is constitutively activated in benign meningiomas and meningioma cell cultures.⁵⁸ Treatment with PD098059, an MEK inhibitor, reduces MAPK phosphorylation, inhibits meningioma growth in vitro, and prevents PDGF-BB stimulation of meningioma growth.⁵⁸ The MAPK pathway is also activated in some, but not all, atypical and malignant meningiomas,⁸¹ suggesting that other signal transduction pathways may also be involved. A number of Raf inhibitors (for example, sorafenib) and MEK inhibitors (for example, PD098059 and AZD6244) are undergoing clinical evaluation and may have roles in the treatment of meningiomas. Activation of Ras requires localization to the cytoplasmic surface of the cell membrane.¹ This subcellular localization is dependent on the

addition of a hydrophobic farnesyl group to the Ras protein, catalyzed by the enzyme farnesyltransferase. Farnesyltransferase inhibitors, such as tipifarnib (Zarnestra, Johnson & Johnson) and lonafarnib (Sarasar, Schering-Plough) inhibit the Ras pathway, and may have therapeutic potential in meningiomas. Nevertheless, preliminary studies suggest that the activity of these agents may be limited in benign meningiomas.⁵⁴

The PI3K/Akt Pathway

The PI3K/Akt pathway plays a central role in many malignancies.^{22,32} Both Akt and p70^{S6K} are expressed and activated (phosphorylated) in benign meningiomas and play a role in signal transduction from PDGFR stimulated by PDGF-BB.⁵⁷ Treatment with a PI3K inhibitor has been found to produce a dose-dependent inhibition of PDGF-BB stimulation, with a concomitant attenuation of Akt and p70^{S6K} phosphorylation.^{54,57} Phospho-Akt is present in higher levels in atypical and malignant meningiomas than in benign meningiomas.⁸¹ Inhibition of PI3K has resulted in reduction in phospho-Akt activity in atypical and malignant meningiomas.⁸¹ These results suggest that the PI3K/Akt pathway may play a central role in meningiomas, especially in atypical and malignant meningiomas. Inhibitors of PI3K (for example, BEZ235), inhibitors of Akt (for example, perifosine), and mTOR inhibitors (for example, sirolimus, temsirolimus [CCI-779], everolimus [RAD001], and AP23573) may have therapeutic potential in these tumors.

The PLC- γ 1-PKC Pathway

In addition to activating the MAPK and the PI3K/Akt pathways, receptor tyrosine kinases such as EGFR and PDGFR also activate PLC- γ 1-PKC.⁵⁴ Activation of PLC- γ 1-PKC results in hydrolysis of phosphatidylinositol-4,5-diacylglycerol to inositol 1,4,5-triphosphate and 1,2-diacylglycerol. The 1,2-diacylglycerol activates PKC and the MAPK and PI3K/Akt pathways.^{54,55} The PKC enters the nucleus and activates c-fos and c-jun, leading to cell proliferation and inhibition of apoptosis.⁵⁴ Activation of EGFR on meningioma cells results in phosphorylation of PLC- γ 1.⁵⁵ The interaction of PLC- γ 1 with the MAPK and the PI3K/Akt pathways underscores the complexities of the signaling pathways and the likelihood that inhibition of multiple targets will be necessary.

The TGF- β -SMAD Signaling Pathways

The precise role of TGF- β in meningiomas remains to be defined. Meningiomas secrete TGF- β 1, 2, and 3, and possess functional TGF- β type I and II receptors.^{54,56} Transforming growth factor- β 1 inhibits proliferation of leptomeningeal and benign meningioma cells via signal transduction through the SMAD 2/3 pathway.^{54,56} In other tumors, including gliomas, higher-grade tumors change from being inhibited to being stimulated by TGF- β .⁵⁴ Whether a similar process occurs in meningiomas is unclear. If TGF- β plays an activating role in high-grade meningiomas, evaluating such inhibitors of TGF- β as SB-431542, AP12009, and GC1008 may be worthwhile.

Cell Cycle Inhibitors

Recently, there has been progress in identifying agents that target the cell cycle to treat cancer.^{124,125} Cyclin-dependent kinase activity can be inhibited by agents that competitively inhibit CDK ATP-binding pockets or that allosterically modulate CDK or endogenous CDK inhibitor complexes. Single-agent activity has been modest to date, but newer oral agents that allow long-term dosing and combinations of CDK inhibitors with other targeted agents or cytotoxic agents may hold greater promise.^{124,125}

Apoptosis Modulators

Defects in programmed cell death (apoptosis) mechanisms play an important role in tumor pathogenesis and resistance to therapy.^{95,113,115,132} Apoptosis occurs via two main mechanisms. The extrinsic pathway is characterized by activation of death receptors with subsequent activation and cleavage of caspase 8. The intrinsic pathway is characterized by depolarization of the mitochondrial membrane, activation of caspase 9 and then caspase 3 and other executioner caspases.^{95,113,115} There has been increasing interest in identifying targeted agents that modulate apoptosis to destroy tumor cells.^{38,95,113,115} This modulation can be achieved either by inhibiting pro-survival pathways such as the Akt and MAPK pathways and NF- κ B, or by inducing apoptosis. The activation of cell surface receptors by TRAIL leads to stimulation of the extrinsic pathway.¹¹⁵ Agents that activate these receptors, such as monoclonal antibodies to TRAIL receptors and recombinant TRAIL, are being evaluated as monotherapies and in combination with chemotherapeutic agents.¹¹⁵

The Bcl-2 family of proteins plays a central regulatory role in the intrinsic pathway. Overexpression of Bcl-2 or Bcl-XL renders tumor cells resistant to apoptotic stimuli, including many cytotoxic agents. Strategies to inhibit these proteins with small molecules such as ABT-737,¹⁰² Bcl-2 antisense,¹⁰⁷ and BH3 mimetic peptides⁷¹ are being evaluated.

The IAPs are endogenous apoptosis suppressors, many of which function as caspase inhibitors.¹¹³ A number of inhibitors of IAPs are in development; they represent a promising class of agents with antitumor activity that may be synergistic with conventional cytotoxic therapies and other targeted molecular agents.^{113,120,121} To date these agents have not been evaluated in meningiomas.

Another class of agents that may have therapeutic potential in meningiomas is synthetic retinoids, such as fenretinide, that induce apoptosis in tumor cells.¹⁰⁹ In an in vitro study, fenretinide induced apoptosis in all three histological subtypes of meningioma and exerted diverse cellular effects, including DR5 upregulation, modulation of retinoid receptor levels, and inhibition of IGF-1-induced proliferation.¹⁰⁹

Inhibition of Angiogenesis

Meningiomas are highly vascular tumors that derive their blood supply predominantly from meningeal vessels supplied by the external carotid artery, with additional supply from cerebral pial vessels.⁶⁸ Inhibition of angiogenesis has become an increasingly important approach to treating cancer.³⁴ Studies evaluating inhibitors of angiogenesis in meningiomas are limited. In one early study,¹⁴⁰ investiga-

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tors found that TNP-470, a fumigillin analogue, inhibits the growth of benign and malignant meningioma xenografts in nude mice.

Vascular endothelial growth factor plays a central role in tumor angiogenesis, and there is increasing evidence that inhibition of VEGF or VEGFR can lead to significant anti-tumor effects.³⁴ Inhibition of VEGF with the anti-VEGF antibody bevacizumab (Avastin, Genentech) has significantly improved survival in several malignancies including colorectal, lung, and breast cancer.⁵³ Inhibitors of VEGFR such as sorafenib (Nexavar, Bayer) and sunitinib (Sutent, Pfizer) have also prolonged survival in patients with renal cell carcinoma and gastrointestinal stromal tumors.⁵³ Vascular endothelial growth factor and VEGFR are expressed in meningiomas, and the level of expression increases with tumor grade.^{39,69,108} Expression of VEGF is increased two-fold in atypical meningiomas and 10-fold in malignant meningiomas compared with benign meningiomas.⁶⁹ Vascular endothelial growth factor also plays an important role in the formation of peritumoral edema, which adds to the morbidity of these tumors.^{39,108} Inhibitors of VEGF and VEGFR are promising agents in meningioma treatment, with the potential not only to inhibit angiogenesis, but also to decrease peritumoral edema. A multicenter Phase II study of sunitinib in patients with recurrent or inoperable meningiomas is expected to open soon at Dana-Farber/Brigham and Women's Cancer Center and Memorial Sloan-Kettering Cancer Center. Sunitinib is a theoretically appealing agent for meningioma treatment because it is a multiple tyrosine kinase inhibitor that targets both VEGFR and PDGFR (in addition to c-Kit and the FLT3 and RET kinases). During each 6-week cycle, patients will receive sunitinib (50 mg/day) daily for 4 weeks followed by 2 weeks without treatment. Levels of serum biomarkers will be assessed, tumor expression profiling will be performed, and perfusion magnetic resonance images will be obtained (although it is not yet clear if the imaging studies will be performed in all cases) with the goal of developing predictors of response. A trial of sorafenib, which also targets VEGFR and PDGFR, is in progress.

Other angiogenic factors implicated in meningiomas include fibroblast growth factor,⁶⁹ placental growth factor,²⁷ and possibly HGF/SF, although the role of the latter is less clear.^{69,79} The presence of HGF/SF and its receptor c-MET appears to be associated with an increased proliferation index and rate of recurrence.⁷⁹

Endothelins are peptides that promote tumor progression by several mechanisms, including angiogenesis, cell proliferation, inhibition of apoptosis, and matrix remodeling. Several isoforms are known, including ET-1, ET-2, and ET-3. The ETs function via two G-protein-coupled receptors, ET-A and ET-B.^{4,47} Both ET-1 and ET-A are overexpressed in meningiomas.^{47,103} The growth of primary meningioma cultures can be blocked by the ET-A inhibitor BQ-123 but not by the ET-B inhibitor RES-701-3, which suggests that the effects of ET-1 on meningioma growth are mediated by ET-A receptors.¹⁰³ Several ET-A receptor antagonists are under development, including astrasentan (Xinlay, Abbott) and ZD4054, but they have not yet been tested in meningiomas.

Inhibition of Invasion

Brain invasion is a characteristic of meningiomas, espe-

cially high-grade tumors.^{68,105} Meningiomas overexpress matrix metalloproteinases, such as MMP-2 and 9,^{99,126} SPARC, tenascin, and stremelysin-3,¹⁰⁵ while malignant meningiomas overexpress TFPI-2.⁶⁵ Tissue factor pathway inhibitor-2 is an extracellular matrix-associated Kunitz-type serine proteinase inhibitor secreted by all vascular cells. It plays a role in tumor invasion and metastasis, presumably by plasmin-mediated matrix remodeling. Previous studies showed that expression of TFPI-2 is lost in high-grade tumors, including gliomas. Transfection of TFPI-2 mRNA into the human meningioma cell line IOMM-Lee inhibited tumor growth in vitro and in vivo, which suggests that TFPI-2 may have therapeutic potential in malignant meningiomas.⁶⁵ Other invasion inhibitors have been studied for the treatment of systemic cancers and gliomas, and some of these agents may have a therapeutic effect in meningiomas.^{70,93,111,117} One such agent is cilengitide, an inhibitor of $\alpha V\beta 3$ and $\alpha V\beta 5$ integrins, both of which are expressed in meningiomas⁵ and are potentially important for angiogenesis and invasion. The drug is in clinical trials for the treatment of gliomas, where it has been well tolerated and appears to show evidence of activity.⁹¹

Other Molecular Targets

Other potentially attractive therapeutic targets in meningiomas include IGFR-2,^{97,98} histone deacetylase,⁷³ NF κ B,⁹⁴ HSP90,⁴² JAK/STAT,⁷⁷ checkpoint kinase,⁷⁶ and possibly Src kinase,⁵⁰ focal adhesion kinase,⁸⁶ and hypoxia-inducible factor 1 α .¹⁰⁰ As with gliomas and other solid tumors, the complexity of the molecular abnormalities in meningiomas and the redundancy of the signaling pathways make it improbable that single agents will achieve the same success as imatinib in CML.¹³² Nonetheless, the use of targeted molecular agents remains a promising and largely unexplored area in the treatment of meningiomas. It will be important to improve our understanding of the molecular pathogenesis of meningiomas and to identify the critical molecular abnormalities driving tumor growth that can be targeted. Multitargeted "dirty" drugs, combinations of targeted agents inhibiting complementary molecular targets, or the combination of targeted agents with conventional cytotoxic agents and especially radiation therapy will lead to greater antitumor effects than single agents alone.^{9,116,132}

The results of preclinical studies suggest that radiation sensitivity can be regulated by growth factors (EGFR, IGFR), signal transduction pathways (Ras/MAPK, PI3K/Akt), checkpoint activation and DNA repair (ATM, Chk1, Rad 51), and apoptosis-related proteins (Fas, Bcl2).⁹ Many of these can be inhibited by targeted molecular agents.

Heat shock protein 90 acts as a molecular chaperone protein that is required for maturation and stability of various client proteins including EGFR, Akt, Raf, p53, and CDK4. By blocking HSP90, 17AAG enhances radiation sensitivity in several tumor cell lines. This agent and other HSP90 inhibitors may have therapeutic potential in meningiomas.^{42,116}

There is also increasing evidence that angiogenesis inhibitors may enhance radiation sensitivity.^{20,132} Possible mechanisms for the beneficial effects of angiogenesis inhibition include direct antitumor effects, endothelial cell radiosensitization resulting in damaged tumor vasculature, and improved oxygenation as a result of elimination of in-

effective tumor vessels and decreased interstitial pressure.¹³⁶ Specific angiogenesis inhibitors with potential radiosensitizing effects include vandetinib (ZD6474), an inhibitor of VEGFR and EGFR; vatalanib (PTK787), an inhibitor of VEGFR and PDGFR; enzastaurin (LY317615), an inhibitor of PKC- β 2 and PI3K/Akt; and bevacizumab, a monoclonal antibody against VEGF.

Hormonal Targets

There has been longstanding interest in the possible role of sex hormones in meningioma growth. This interest is the result of several observations: 1) Meningiomas are twice as common in women. 2) Increased growth of meningiomas may occur in pregnancy and in the luteal phase of the menstrual cycle. 3) The incidence of meningiomas is slightly increased in patients with breast cancer.^{7,68} Estrogen receptors are present at low levels in approximately 10% of meningiomas, while progesterone and androgen receptors are present in approximately two thirds of meningiomas and are more frequently expressed in women than in men.^{52,68,83,119} Progesterone receptors are expressed predominantly in benign meningiomas with low proliferation indices;¹³⁷ they are infrequently expressed in atypical and malignant meningiomas. Because meningiomas express only low levels of estrogen receptors, the expression of progesterone receptors is probably not regulated in an estrogen-dependent manner, as is the case in breast cancer.¹⁰⁵

Over the past two decades there have been several studies evaluating antihormonal agents in meningiomas. Given the low level of estrogen receptor expression, it is not surprising that studies with antiestrogens did not show any efficacy.^{41,78} In one study of tamoxifen for refractory meningioma, partial or minor responses were observed in three of 19 patients.⁴¹ Because of the high likelihood of progesterone receptor expression in most meningiomas, there has been substantial interest in progesterone receptor inhibitors.⁴³ Initial studies of the antiprogestosterone agent mifepristone (RU486) were encouraging. In one study, four of 14 patients had a minor decrease in the size of the tumor, and one patient had objective clinical improvement.⁴⁵ In another study three of 10 patients experienced stabilization of disease with mifepristone treatment and tumor size decreased minimally in another three.⁶⁷ Nevertheless, a prospective randomized multicenter study conducted by the Southwest Oncology Group failed to demonstrate any treatment effect; the median survival was 31 months, and 42 of 45 patients experienced disease progression with a median time to progression of 6 months.⁴⁴ Mifepristone's lack of efficacy may be explained in part by the loss of progesterone receptor expression observed in meningiomas with increased proliferation index and histological grade. This is relevant because patients who are enrolled into clinical studies are more likely to have these advanced types of tumors than other types.

To date there have been no published trials of androgen receptor antagonists in meningiomas. In a small unpublished study conducted at Brigham and Women's Hospital, no responses were seen in six patients with recurrent meningiomas treated with the anti-androgen flutamide, although two patients experienced disease stabilization for almost 1 year.

There has been interest in the effect of GH on meningiomas since the initial observation that the incidence of

meningiomas may be increased in patients with acromegaly.¹¹⁰ Growth hormone secreted by the pituitary gland stimulates the synthesis of IGF-1 in the liver, and together they facilitate normal growth.¹¹⁰ Growth hormone receptors are ubiquitous in meningiomas, and GHR inhibition decreases tumor growth.^{35,36,84,110} Pegvisomant, a pegylated GH analog that acts as a competitive GHR antagonist, significantly inhibited the growth of meningioma xenografts in nude mice.⁸⁴ Tumor IGF-1 concentrations did not vary with pegvisomant treatment, and there was no autocrine IGF-1 production by the tumors. The antitumor effect was thought to be a consequence of decreased IGF-1 in the circulation or surrounding host tissue or both. Direct blockade of the GHR on tumor cells may also contribute to the anti-tumor effect. Whether pegvisomant can inhibit meningioma growth in patients remains to be established. In a single patient with acromegaly and a meningioma, the tumor continued to grow despite several years of treatment with pegvisomant.²⁸

Somatostatin receptors, especially the sst2A subtype, are present on most meningiomas, although their functional role remains unclear. The addition of somatostatin inhibits meningioma growth in vitro in some studies, but increases meningioma proliferation in others.¹³ Radiolabeled octreotide, a long-acting somatostatin agonist, has been used in imaging studies of meningiomas.^{48,64} There have been anecdotal reports of octreotide inhibiting growth in human meningiomas,³⁷ but the results are difficult to interpret in light of very small numbers. In a recent study, seven patients with recurrent meningiomas were treated with a sustained-release somatostatin preparation (Sandostatin LAR, Novartis).³³ Indium 111-octreotide single photon emission computed tomography scanning was used to confirm the presence of somatostatin receptors in the tumors. Patients received monthly injections of sustained-release somatostatin (20–30 mg/month). Four of the seven patients experienced clinical and radiographic responses. A large-scale trial evaluating this approach is in progress.

Pasireotide (SOM230) is a novel, orally administered, 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 just described.⁸ A Phase II trial for patients with recurrent or progressive meningiomas is planned. Biomarkers that may serve as predictors of efficacy or toxicity will be evaluated in all patients.

Looking to the Future

As the numbers of potential molecular targets, targeted agents, and drug combinations increase dramatically, our ability to evaluate agents preclinically and to select only the most promising ones for clinical trials becomes increasingly important. This is especially imperative for meningiomas because the relevant patient population is small and limited resources have been devoted to the study of this tumor. Further development of predictive meningioma cell lines and animal models for screening drugs is crucial. Clinical trial designs must be optimized with increased use of tumor tissue to verify that adequate drug levels are achieved in the tumor and that putative targets are appropriately inhibited in vivo. Additionally, more effective correlations of response to treatment and tumor genotype must

be routinely included in clinical trials of targeted agents. These data will ultimately enable physicians to individualize targeted drug choices on the basis of the tumor's genetic profile.

Conclusions

Despite advances in surgery, radiation therapy, and radiosurgery, there remains a small but important subset of patients with meningiomas in whom the disease recurs and in whom the recurrent tumors are refractory to conventional therapies. Chemotherapies have minimal activity and hormonal therapies have proven to be largely ineffective. Progress in identifying alternative forms of therapy for these patients with recurrent meningiomas has been limited by poor understanding of the molecular pathogenesis of meningiomas and of the critical molecular changes driving tumor growth, as well as by the lack of meningioma cell lines and tumor models for preclinical studies. There is significant experience with targeted molecular agents for systemic cancers and malignant gliomas which may be translated into effective strategies for meningiomas. It is hoped that these novel therapies will complement the traditional approaches and lead to more effective treatment for patients with meningiomas.

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Address correspondence to: Patrick Y. Wen, M.D., Center for Neuro-Oncology, Dana-Farber/Brigham and Women's Cancer Center, SW430D, 44 Binney Street, Boston, Massachusetts 02115. email: pwen@partners.org.