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TOPIC REVIEW

Chemotherapy, hormonal therapy, and immunotherapy for recurrent meningiomas

Chrissa Sioka · Athanassios P. Kyritsis

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Abstract Meningioma is a common intracranial tumor, originating from the meninges of the skull or spinal canal. Most meningiomas are benign tumors, however atypical or anaplastic tumors can be found in 6% of cases. Patients with asymptomatic small benign meningiomas can be followed without therapy, but in symptomatic patients complete surgical resection should be performed. For recurrent previously resected tumors re-resection is recommended followed by radiotherapy in selected cases. Antiprogesterone treatment can also be considered in recurrent benign meningiomas. Immunotherapy with interferon-alpha and chemotherapy should be reserved for all cases of recurrent meningiomas (benign, atypical, and malignant) when all the standard therapies have failed or contraindicated.

Keywords Chemotherapy · Meningioma · Progesterone · Hydroxyurea · Interferon

Introduction

According to the World Health Organization (WHO) meningiomas are classified as benign meningiomas (grade I), atypical meningiomas (grade II), and anaplastic meningiomas (grade III) [1]. A frequent finding in meningiomas is expression of progesterone and epidermal growth factor receptors; however, expression of estrogen or androgen receptors is less consistent. Patients with asymptomatic small benign meningiomas can be followed with imaging studies without surgery. In symptomatic patients complete surgical resection is often curative. For recurrent previously resected tumors reoperation is recommended followed by radiotherapy. Atypical and malignant meningiomas should be resected followed by adjuvant radiotherapy. Medical treatments such as hormonal therapy, interferon-alpha, and chemotherapy may have some role in the management of recurrent unresectable meningiomas [1, 2].

C. Sioka (✉) · A. P. Kyritsis
Neurosurgical Research Institute, University of Ioannina School of Medicine, University Campus, Ioannina 45110, Greece
e-mail: csioka@yahoo.com

C. Sioka
Department of Nuclear Medicine, University Hospital of Ioannina, Ioannina 45110, Greece

A. P. Kyritsis
Department of Neurology, University Hospital of Ioannina, Ioannina 45110, Greece

Biologic aspects potentially helpful for therapy

In meningioma, heterogeneous expression of P-glycoprotein (Pgp), multidrug resistance protein (MRP1), lung resistance protein (LRP), and O6 methylguanine-DNA methyltransferase (MGMT) was reported, suggesting that analysis of these factors may be important during selection of a chemotherapy regimen [3]. In a case report with recurrent malignant meningioma in which reverse-transcription polymerase chain reaction (RT-PCR) assay of the recurrent tissue revealed overexpression of multidrug resistance (MDR1), MRP1, MRP2, and MGMT mRNA, but no ATP-binding cassette G (ABCG 2) expression, the patient was given mitoxantrone and hydroxyurea following irradiation, after which the tumor did not recur for 3 years. The authors of that report suggested that individual chemotherapy based on mRNA expression of drug-resistance gene may be necessary for the treatment of recurrent malignant meningioma [4].

Upregulation of cyclooxygenase-2 (COX-2), the inducible form of the enzyme involved in the first steps of the prostaglandins and thromboxane synthesis, has been demonstrated in the majority of meningiomas [5, 6], indicating that it may modulate tumoral progression, multidrug resistance, and angiogenesis. In addition, celecoxib, a COX-2 inhibitor, inhibited meningioma growth in vitro in a dose-dependent fashion [6], and in vivo in a mouse xenograft model associated with apoptosis and reduction of tumor vascularity [7]. Thus, there may be a possible therapeutic use of the COX-inhibitors nonsteroidal anti-inflammatory drugs (NSAIDs), which can block tumor growth through many mechanisms, especially through antiangiogenic and proapoptotic effects. Moreover, NSAIDs can also improve the efficacy of radiotherapy, chemotherapy, and hormonal therapy [5].

Lovastatin inhibits 3-hydroxy 3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme for synthesis of mevalonic acid, a precursor for cholesterol, farnesyl, and geranylgeranyl pyrophosphate isoprenoids. Posttranslational farnesyl or geranylgeranylation of low-molecular-weight guanosine 5′-triphosphate (GTP)-binding proteins such as RAS and RHO are thought to be an essential step in activation of phosphorylation cascades such as the RAS-RAF-1-MAPK/ERK kinase (MEK)-1-mitogen-activated protein kinase/extracellular regulated kinase (MAPK/ERK) pathway which stimulate cell proliferation. The effect of lovastatin on cell proliferation was assessed in eight human meningioma cell cultures, where it inhibited platelet derived growth factor-BB (PDGF-BB), cerebrospinal fluid (CSF), and fetal bovine serum (FBS) stimulation of [3H]-thymidine incorporation and cell proliferation, and reduced phosphorylation/activation of MEK-1/2 and MAPK/ERK. This study suggested that lovastatin represents a potent inhibitor of meningioma cell proliferation and recommended further studies to assess whether lovastatin and similar HMG-CoA reductase inhibitors may be a new adjunctive chemotherapy for recurrent meningiomas [8].

Presence of expression of granulocyte cell stimulating factor (G-CSF), macrophage colony stimulating factor (GM-CSF) and their respective receptors in meningiomas but not in normal meningeal cells was correlated significantly with enhanced cell proliferation in the tumor and higher malignancy, suggesting a contribution of both factors to tumor progression [9]. Thus, use of these agents should be avoided during immunosuppression from chemotherapy if possible, since they can potentially activate tumor growth.

DNA ploidy and S-phase—as determined by DNA flow cytometry—are useful indicators of the biological behavior of meningiomas. (99 m)Tc-Tetrofosmin brain single photon emission computerized tomography (SPECT) may have the ability to discriminate benign meningiomas from malignant meningiomas preoperatively, since there is reliable correlation between tracer uptake and the percentage of the cell fraction on S-phase and the level of aneuploidy and tumor grade [10, 11]. Thus, use of these techniques preoperatively can guide the clinician to select the appropriate therapeutic option.

Chemotherapy

Management of unresectable progressive meningioma remains a challenge since therapeutic options are limited (Table 1). A prospective phase II study of temozolomide (TMZ) in 16 patients with refractory meningioma previously treated with surgery and radiotherapy was ineffective. Eight patients with CSF dissemination of previously treated meningiomas, that received both systemic chemotherapy (temozolomide in four patients, irinotecan in three patients, hydroxyurea in three patients, interferon-alpha in two patients, and doxorubicin plus ifosfamide in one patient) and intraventricular chemotherapy (liposomal cytosine arabinoside in seven patients, thiotepa in one patient, and busulfan in one patient) showed modest outcomes with stable disease in seven patients and progressive disease in one patient. The response duration ranged from 2 to 31 months (median 3.5 months) [12].

Hydroxyurea inhibits ribonucleotide reductase and can induce apoptosis in meningioma cell cultures and animal models. The first evidence that meningiomas respond to treatment with hydroxyurea was obtained in four patients with recurrent and unresectable meningiomas who responded favorable to the treatment [13]. Treatment of 16 evaluable patients with unresectable or residual meningioma with hydroxyurea (20 mg/kg/day orally) resulted in 14 patients with stable disease (88%) ranging from 20 to 144+ weeks (median 80 weeks) and 2 patients with progressive disease. Toxicity was hematologic in most, with nine patients (53%) requiring dosage reductions. This study showed that hydroxyurea had modest activity against meningiomas and that it should be considered in patients

Table 1 Treatment options for recurrent meningioma after failure of surgery and radiotherapy

Chemotherapy	Hydroxyurea, 20 mg/kg/day
Immunotherapy	Interferon-alpha-2B, 4 million units/m^2 per day, 5 days per week
Hormonal therapy	Mifepristone, 200 mg/day PO Tamoxifen, 40 mg/m^2 b.i.d. for 4 days, then 10 mg/m^2 b.i.d.
Somatostatin analogues	Sandostatin LAR, 30 mg IM every 28 days

PO per os, LAR long-acting release, IM intramuscular

with unresectable tumors or large residual tumors following surgical resection [14]. The same investigators in an enlarged cohort of patients (21) with extended follow-up reported 90% stabilization rate ranging from 20 to 328+ weeks (median time to progression (TTP) 176 weeks) [15].

In another study, hydroxyurea at 20 mg/kg/day was administered to 11 women and 9 men with recurrent or unresectable intracranial meningiomas (16 benign, 3 atypical, and 1 malignant). All patients had received previous radiotherapy. In 12 patients with benign meningiomas the tumor was stabilized (median duration of treatment 122 weeks, range 8–151 weeks), one patient had a minor response, and three patients showed progression. All four patients with either atypical or malignant meningioma progressed through chemotherapy [16]. To test the benefit of hydroxyurea in the treatment of recurrent and nonresectable slow-growing meningiomas, 12 patients were treated for 2 years with continuous chemotherapy with hydroxyurea, 20 mg/kg/day. One minimal response was documented by computerized tomography (CT), accompanied by clinical stabilization. Nine patients showed progressive disease, with median time to progression of 13 months (range 4–24 months). Two other patients were removed from the study secondary to hematological toxicity. Thus, in this series hydroxyurea was not effective for treatment of nonresectable slow-growing meningiomas [17]. In another small study, five patients with symptomatic recurrent or residual meningiomas and one with an unresectable meningioma received hydroxyurea for 1 year, starting at a dose of 15 mg/kg/day. No tumors reduced in size and three remained stable. Three experienced significant drug-related side-effects [18]. A prospective phase II study of hydroxyurea in 36 patients with recurrent meningioma showed 5.6% objective responses, 36% stable disease, and 58% progression. The conclusions of that study were that hydroxyurea has marginal efficacy for meningioma and should not be considered as an alternative if radiotherapy or surgery is feasible [19]. Twenty-one patients with recurrent or progressive meningiomas received treatment by fractionated 3d-conformal radiation (55.8–59.4 Gy) and concurrent hydroxyurea, administered for a median time of 3 months with a daily dosage of 20 mg/kg. Disease stabilization was achieved in 14/21 patients, and progression-free survival rates at 1 and 2 years of 84% and 77%, respectively [20].

The effects of the topoisomerase I inhibitor irinotecan (CPT-11) on cellular proliferation in primary meningioma cultures and the IOMM-Lee malignant meningioma cell line were evaluated in vitro and an in vivo subcutaneous murine tumor model. The results showed that irinotecan demonstrated growth-inhibitory effects both in vitro and in vivo, suggesting that it may play a role in the treatment of atypical or malignant meningiomas [21]. However, a prospective phase II study of irinotecan in 16 adult patients with recurrent surgery and radiotherapy-refractory WHO grade I meningioma failed to demonstrate efficacy [22].

Somatostatin receptors (five subtypes, SSTR 1-5) are present on most meningiomas [23, 24], and their activation has been associated with an antiproliferative effect in vitro [25, 26], possibly through an inhibitory effect on cyclic adenosine monophosphate (cAMP) formation [27]. A prospective pilot trial of sustained-release somatostatin (Sandostatin LAR) was conducted in 16 patients with recurrent meningiomas (positive somatostatin receptors) who received 2–15 monthly cycles of somatostatin with minimal toxicity. Thirty-one percent of patients demonstrated a partial radiographic response and 44% achieved progression-free survival at 6 months, suggesting that somatostatin analogues may offer a novel alternative treatment for recurrent meningiomas [28].

Immunological therapy

There has been accumulating evidence from in vitro and in vivo studies, that interferon (IFN)-alpha may be active against meningiomas. Addition of low concentrations of IFN-alpha to meningioma cell cultures produced a 70–100% inhibition of thymidine DNA incorporation [29]. Wober-Bingol et al. reported a marked effect of IFN-alpha-2B on one patient with meningioma [30].

In a preliminary study in six patients with recurrent unresectable or malignant meningiomas a recombinant interferon alpha-2B (IFN-alpha-2B) was administered at a dosage of 4 mU/m^2/day, 5 days per week. Two of these meningiomas were histologically benign, one was atypical, and three were malignant. Five of six patients exhibited positive response to treatment, with stabilization of the tumor in four patients and slight regression in one, lasting from 6 to 14 months [31]. Another similar study reported stable disease in 9 of 12 patients. Three of the nine patients were followed for relatively long times (8, 8, and 4.5 years). Furthermore, [^{11}C]-L-methionine positron emission tomography (PET) scans were able to predict responses and the suitability of patient for long-term treatment [32]. These results suggest that IFN-alpha can produce long-lasting remissions in rapidly progressing atypical and malignant meningioma, and may represent a valid therapeutic option for patients with recurrent or unresectable tumors.

Hormonal therapy

Several factors suggest that sex hormones, i.e., progesterone, estrogen, androgen, may play a role in stimulating the

growth of meningiomas. A previous study found progesterone receptors in 76% and estrogen receptors in 19% of meningiomas. However, these receptors were mostly present in benign tumors, and aggressive meningiomas were accompanied by low numbers or absence of progesterone receptors [33].

Mifepristone (RU486), an antiprogesterone agent, was shown to inhibit the growth of meningioma cells in vitro [34]. Two early small trials with this agent showed stabilization or minor decrease in the size of the tumor in about half of the patients [35, 36]. Twenty-eight patients with unresectable meningioma were treated with oral mifepristone 200 mg/day with median duration of therapy of 35 months (range 2–157 months). Repeated oral administration was well tolerated except for mild fatigue (22 patients), hot flashes (13 patients), and gynecomastia/breast tenderness (6 patients). In addition, three patients developed endometrial hyperplasia and one patient peritoneal adenocarcinoma after 9 years of therapy. Minor responses were noted in eight patients, seven of whom were male or premenopausal female [37].

Although the expression of estrogen receptors is less consistent, tamoxifen, an antiestrogen agent, induced transient stabilization or minor response in nine of ten patients with recurrent unresectable meningiomas [38]. In a case report of a patient with a meningioma after no recurrence of a previously treated gastric carcinoma, the antiestrogen agent mepitiostane was administered. This agent resulted in a marked regression (73%) of the meningioma 2 years after initiation of therapy [39].

Use of calcium channel blockers

Since a large proportion of meningiomas contain receptors for platelet-derived growth factor and epidermal growth factor that promote the proliferation of meningioma cells in culture, alterations in intracellular calcium could interrupt this pathway and decrease cellular proliferation. Primary meningioma cell cultures were given growth factors and/or various calcium channel antagonists, and a dose-response decrease in cell growth was seen when verapamil, nifedipine, or diltiazem (voltage-dependent calcium channel-blocking agents) was added to serum-containing media [40]. It was shown that that the calcium channel antagonists' growth inhibition was due to interference with the intracellular signaling pathways of cultured meningioma cells, an effect unrelated to voltage-sensitive calcium channels [41]. Thus, addition of calcium channel antagonists to chemotherapeutic drugs could enhance tumor growth inhibition. Further experiments in primary and malignant meningioma cell lines treated with either hydroxyurea, RU486, and the addition or not of diltiazem or verapamil and subsequent implantation into nude mice were performed. The addition of diltiazem or verapamil to hydroxyurea or RU486 augmented meningioma growth inhibition both in vitro, by inducing apoptosis and G1 cell-cycle arrest, and in vivo, by decreasing proliferation and microvascular density. These results suggested a possible role for calcium channel antagonists as an additional therapy for recurrent or unresectable meningiomas [42, 43].

Extracranial metastases

Extracranial metastases of meningiomas are well documented, occurring usually with local recurrence of the tumor. Metastases to all organ systems have been reported, but the most common sites are lung, bone, liver, and lymph nodes [1]. There are no clear guidelines for the treatment of metastatic meningiomas. Surgery, radiotherapy, chemotherapy, and biological therapy can be used alone or in combinations according to each case, but prognosis is usually poor.

Conclusion

Meningioma, although usually a benign tumor treated effectively with surgery, may be difficult to manage at recurrence. If repeated surgeries or radiotherapy fail to attain local control, hormonal therapy, immunotherapy or chemotherapy may be indicated. Antiprogesterone and antiestrogen agents alone, or in combination with calcium channel blockers, could be beneficial for a period of time in recurrent benign meningiomas. Interferon-alpha or chemotherapy should be considered in all recurrent meningiomas (benign, atypical or malignant) after failure of all other treatments. Hydroxyurea is the most commonly used chemotherapeutic agent, although other drugs can be used after further recurrence. Further studies should be conducted in order to establish the role of somatostatin, lovastatin, and nonsteroidal anti-inflammatory drugs in the management of recurrent meningiomas.

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