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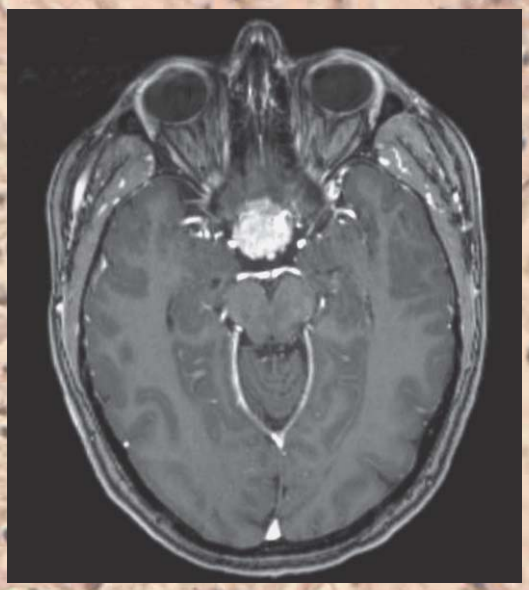

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Drug Therapy for Recurrent, Progressive, Atypical, and Malignant Meningiomas

Christine Marosi

Abstract: So far, no breakthrough for systemic therapy of recurrent meningiomas has been achieved. Despite a multitude of optional drugs there is so far no standard of care. On the other hand, although the disease is rare, each neuro-oncological centre is faced with some patients with unmet treatment needs.
Future attempts of drug therapy in meningiomas should be planned for the distinct subgroups of these heterogeneous tumours. Cohort studies should be able to answer the question of whether meningiomas occur more rarely or do not become symptomatic in individuals under treatment with statins, glitazones, or calcium channel blockers. If found effective, such drugs would be suitable as first-line treatment in patients with grade-I recurrent meningiomas, as for these indications most probably long treatment periods appear necessary. For patients whose tumours recur with such drugs, oral mTor antagonists such as everolimus or targeted therapies could potentially represent further treatment options which should be evaluated in multicentre phase-II studies, whereas cytotoxic drugs with severe side effects such as trabectedin could perhaps be investigated for recurrent malignant meningiomas after all other options have been exhausted. **Eur Assoc NeuroOncol Mag 2013; 3 (3): 128–31.**

Key words: meningioma, statin, tyrosine kinase inhibitor

Introduction

Only a minority of patients with meningioma are referred to neuro-oncologists for therapy. Nevertheless, this task is challenging as there is currently no established therapy for patients with recurrent, progressive, or malignant meningiomas.

Meningiomas are the most frequent primary brain tumours but their incidence might still be underestimated [1] as the VITA study, a cohort study on healthy elderly people, showed a twice-as-high incidence of indolent meningiomas in asymptomatic women aged 75 years [2], corresponding to a calculated prevalence of 2800/100,000 clinically silent meningiomas in 75-year-old women. The incidence of meningiomas increases with age, with a peak incidence in the sixth decade [3, 4]. A large series on > 1600 patients with meningiomas who underwent surgery in a single centre showed that non-skull-based location and age > 65 years were independent risk factors for higher-grade meningiomas with ORs of 1.779 and 1.5, respectively [5].

The main part of meningiomas can be curatively resected. Modern microneurosurgery has developed with the challenge of refining the techniques of resection of "difficult" meningiomas. However, some meningiomas cannot be resected due to their involvement of vital structures; some WHO grade-I meningiomas recur after surgery, as do atypical and malignant meningiomas. Most of them respond to radiation, either fractionated radiotherapy or radiosurgery.

Still, some meningiomas exhaust all local therapies and patients require systemic treatment. Those patients have usually undergone several neurosurgical procedures and repeated courses of radiotherapy and/or radiosurgery when they are presented to the neuro-oncologist, usually because of ongoing progression of a far advanced disease. Most of these patients are heavily symptomatic from their meningiomas, presenting with pain, neurological deficits, and meningioma-related seizures. These patients may already receive treatment for their seizures as well as against pain and often against depression.

During the last years, basic research has elucidated the pathways associated with the proliferation and recurrence of meningiomas [6–16], providing better understanding of the pathophysiology of meningiomas and suggesting potential therapeutic targets. In this review, data accumulated on systemic treatment of meningiomas will be briefly reviewed and the potential development of systemic therapies reflected.

Genetic Background

Meningiomas were one of the first solid tumours in which a characteristic genetic aberration, a deletion from the long-arm chromosome 22, was found [17]. This aberration leads to loss of the tumour suppressor gene coding for the neurofibromatosis 2 tumour suppressor gene product (Merlin) which has been found in up to 40–60 % of sporadic meningiomas. Merlin is a negative regulator of the mTor complex 1 and positive regulator of mTor complex 2, resulting in cell proliferation [18–20]. These findings imply that antagonising mTor could be a successful therapeutic strategy in meningiomas depending on mTor deregulation. In fact, at the 2012 meeting of the European Society of Medical Oncology (ESMO) 2 groups presented in vivo models where mTor inhibition by everolimus or by everolimus plus octreotide showed an inhibitory effect on mouse meningiomas [21, 22]. Currently, one clinical trial with everolimus in recurrent or progressive meningiomas is listed at www.clinicaltrials.gov.

Treatment

There is no established or approved systemic treatment for patients with recurrent, progressive, atypical, or malignant meningiomas that has shown efficacy in a randomized controlled trial. Nevertheless, 3 systemic treatments – hydroxyurea, interferon-α, and somatostatine analogues – are listed for the treatment of recurrent meningioma by the Central

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Nervous System National Comprehensive Cancer Network (CNS NCCN, 2012) guidelines [23].

Most of the published experience relies on small (often retrospective and monocentric) series or case reports. Interpretation of these small studies is difficult, as they often include very heterogeneous patient samples as well patients with recurrent WHO grade-I meningiomas as well as with atypical and malignant meningiomas which have indeed a different prognosis, furthermore patients who are at different stages of their illness trajectory, either newly diagnosed atypical or anaplastic meningiomas or after failure of one or multiple radiation therapies, which also has to be considered before interpreting outcomes of a given intervention. The compilation of all those different meningioma patient categories has to be seen in the context of the rarity of the disease and of the lack of interest of potential sponsors for trials for meningioma patients.

Recurrent, progressive, atypical, or malignant meningiomas are orphan diseases – only a joint effort of an international study group would succeed in recruiting patients for a pivotal study to test a promising hypothesis. Even the treatments recommended by the NCCN guidelines rely on a low evidence level.

Unlike gliomas, meningioma vessels do not have a blood-brain barrier and circulating drugs penetrate into the meningiomas. However, potentially increased intratumoural pressure in the meningioma could be high enough to preclude the penetration of drugs from the blood stream eg in meningiomas, causing large rims of vasogenic oedema.

Another factor to be considered before initiating and evaluating drug therapies for these patients is that most of them present with complex medications involving enzyme-inducing antiepileptic drugs, non-steroidal antirheumatic drugs against pain, and drugs that might modify intestinal resorption of other drugs such as proton pump inhibitors. So the bioavaibility of any study drug might be heavily affected by the often extensive co-medication of this patient subgroup.

Appreciation of the systemic therapeutic options of systemic therapy in meningiomas has been reviewed in re-evaluated repeatedly in the last years [24–29] and in the current issue by Simó et al [30].

It would be of no benefit to repeat that hormonal treatment with mifepristone has been found ineffective [31] or that only patients without gall stones might benefit from somatostatine analogues for a limited time [32–34], the same is true for interferon-α that might show some activity but often has to be stopped because of severe depression and other psychiatric side effects [35–41] and that the evidence of any difference between the natural course of disease and hydroxyurea (HU) treatment in meningiomas has not been shown so far [42–52]. The "success" of hydroxyurea in "difficult-meningioma" patients is easily understood as the drug is given at half of the dose used to treat myeloproliferative disorders, thus usually very well-tolerated, orally applicable, easily available, and cheap. Most other cytostatic drugs – temozolomide, CAV (cyclophosphamide, adriamycine, vincristin), or irinotecan – [24, 25, 53–55] that have been given alone or in combinations have not reached even this level of evidence in meningioma patients. Recently, hydroxyurea has been tested in combination with targeted therapy or with a calcium antagonist inhibiting p-glycoprotein with more effectivity than HU alone [56, 57], leaving the question of whether HU is effective in meningioma patients unanswered.

For patients with very advanced anaplastic meningiomas, trabectedin, a novel marine cytostatic drug approved for the use in soft-tissue sarcomas and ovarian cancer, might be an ultimate option when all other less toxic therapies have failed, as there is a case report on the use of this drug in a single patient with advanced anaplastic meningioma with additional in vitro experiments showing effectivity of the drug in cell lines of atypical and malignant meningiomas [58].

Targeted Therapies

Over the last years, basic science has shown that meningiomas express potential drug targets on their cell membranes [9, 59–64]. Due to the lack of efficacy of treatment strategies against recurrent, progressive, atypical, and malignant meningiomas, targeted therapies interfering with potential targets identified in progressive meningiomas were investigated as soon as they became available. Formal prospective studies are rare; the present state appears more like a hypothesis-finding phase hopefully preceding a phase with intense study activity.

Imatinib

It has been known for a long time that meningiomas express platelet-derived growth factor beta (PDGF-β) and that meningioma proliferation is stimulated by autocrine growth stimulation loops [59, 65–67]. Therefore, it was obvious to try treatment of recurrent meningiomas with molecules targeting the PDGF-Rα and the first available was imatinib.

The first data on 23 heavily pre-treated patients (13 benign, 5 atypical, and 5 malignant meningiomas) were disappointing with a progression-free survival (PFS) of only 2 months [68]. Reardon et al [56] treated 21 patients with hydroxyurea and imatinib, PFS6 was 61 %. Our own experience on 9 patients is favourable [69] but we observed a severe, fortunately reversible episode of hepatic toxicity in one patient [56, 68].

Gefitinib and Erlotinib

As the epidermal growth factor is often over-expressed, 25 patients with recurrent meningiomas (8 meningiomas WHO grade I, 9 atypical and 8 malignant meningiomas) were treated using either gefitinib (500 mg/day) or erlotinib (150 mg/day). For benign tumours, PFS6 was 25 % and PFS12 13 %. For atypical and malignant meningiomas, PFS6 was 29 % and PFS12 18 %. 32 % of patients maintained stable disease. Nevertheless, the authors considered treatment with epithelial growth factor antagonists as ineffective [70].

Bevacizumab

Recurrent meningiomas show increasing microvascular density and VEGF expression, suggesting a potential role of

neoangiogenesis in the proliferation of meningiomas [71–74]. Drugs targeting VEGF-R have been used in recurrent meningiomas, mainly in case studies [72, 75]. Based on our own experience, bevacizumab induces rapid clinical improvement in patients with significant peritumoural oedema. In a retrospective trial on 14 patients, PFS6 was observed in 86 %, but also one cerebral haemorrhage and one gastrointestinal perforation [76].

Multikinase Inhibitors

Several other inhibitors of PDGF are undergoing evaluation, including sunitinib, MLN518, dasatinib, AMN 107, pazopanib, sorafenib, CP673451, and CHIR 265; 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 but also present a higher risk for side effects [77].

Other Drugs

There are drugs approved for other clinical conditions showing efficacy against meningioma cell lines or primary cell cultures of meningiomas in vitro which have so far not been followed by in vivo testing or clinical trials [78].

Calcium Channel Antagonists

Calcium channel antagonists such as nifedipine, diltiazem, and verapamil can block calcium-mediated growth signals to PDGF-R and other growth factors expressed by meningiomas. It could be shown that meningiomas in patients treated with calcium channel blockers were generally smaller and less vascularised than those found in other patients [79].

AKBA

Park et al [80, 81] report that resin of the incense tree, acetyl-11-keto-beta-boswellic acid (AKBA), has been identified as an orally available inhibitor of topo-isomerase I and II and of lipooxygenase. AKBA showed potent cytotoxic activity on primo cell cultures of 11 meningiomas in the concentration of 2–8 µM/l.

Statins and Glitazones

A different approach was tested by Gehring et al on 2 cell lines of malignant melanoma and 2 cell lines from benign meningiomas [82–85]. They investigated the antiproliferative and even cytotoxic effects of drugs used to control hyperlipidemia and non-insulin-dependent diabetes mellitus, alone and in combination.

Statins inhibit the rate-limiting step of hepatic cholesterol synthesis, thus indispensable for dividing normal or tumour cells. Moreover, statins are known to regulate Ras and Rho, inhibiting the activation of the mitogen-activated protein kinase pathway (MAPK).

Glitazones (thiazolidinediones) are drugs used for decreasing insulin resistance in diabetes mellitus type 2, but they have also been shown to induce cell cycle arrest, differentiation, and/or apoptosis in tumour cells in vitro by induction of reactive oxygen species (ROS).

Gehring et al [82] used both drugs alone and in combination and were able to demonstrate a synergistic proapoptotic effect of simvastatin with proglitazone in meningioma cell lines and will try their promising hypothesis in an orthotropic mouse model. It would be appealing to test such hypotheses in case control studies on patients with meningiomas whose medication is recorded. If meningioma recurrence is less frequent in patients with statins and/or glitazones and calcium antagonists which the patients received to treat diabetes and/or hypertension, prospective trials to prevent meningioma recurrence with these well-known and well-tolerated drugs should be planned. A multinational platform such as EANO could potentially endorse such a project.

Summary

To date, no breakthrough for systemic therapy of recurrent meningiomas has been achieved. The multitude of optional drugs shows that none of them so far could become a standard of care. On the other hand, although the disease is rare, each neuro-oncological centre has some patients with unmet treatment needs.

Future attempts of drug therapy in meningiomas should be planned for the distinct subgroups of these heterogeneous tumours. Cohort studies should be able to answer the question of whether meningiomas occur more rarely or do not become symptomatic in individuals under treatment with statins, glitazones, or calcium channel blockers. If found effective, such drugs would be suitable as first-line treatment in patients with grade-I recurrent meningiomas, as for these indications most probably long treatment periods appear necessary. For patients whose tumours recur with such drugs, oral mTor antagonists such as everolimus or targeted therapies could potentially represent further treatment options which should be evaluated in multicentre phase-II studies, whereas cytotoxic drugs with severe side effects such as trabectedin could perhaps be investigated for recurrent malignant meningiomas after all other options have been exhausted.

Conflict of Interest

None.

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