

European Association of NeuroOncology Magazine

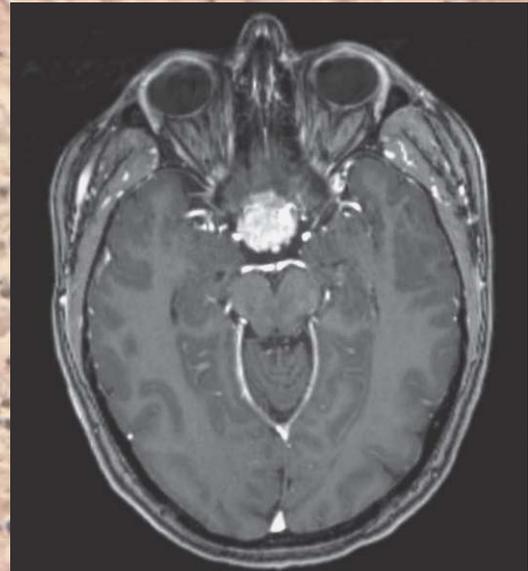
Neurology · Neurosurgery · Medical Oncology · Radiotherapy · Paediatric Neuro-oncology · Neuropathology · Neuroradiology · Neuroimaging · Nursing · Patient Issues

Drug Therapy for Recurrent Progressive, Atypical, and Malignant Meningiomas

Marosi C

European Association of NeuroOncology Magazine 2013; 3 (3)

128-131



Homepage:

[www.kup.at/
journals/eano/index.html](http://www.kup.at/journals/eano/index.html)

Online Database Featuring
Author, Key Word and
Full-Text Search



THE EUROPEAN ASSOCIATION OF
NEUROONCOLOGY

Member of the  DOAJ

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 op-

tions 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 somatostatin analogues – are listed for the treatment of recurrent meningioma by the Central

Received on March 27, 2013; accepted after revision on May 3, 2013; Pre-Publishing Online on May 23, 2013

From the Department of Internal Medicine I, Medical University of Vienna, Austria

Correspondence to: Christine Marosi, MD, Department of Internal Medicine I, Medical University of Vienna, Währinger Gürtel 18–20, 1090 Vienna, Austria; e-mail: christine.marosi@meduniwien.ac.at

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 as 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 anti-inflammatory drugs against pain, and drugs that might modify intestinal reabsorption of other drugs such as proton pump inhibitors. So the bioavailability 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 somatostatin 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, adriamycin, 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-R α 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

neovascularization 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 lipoxygenase. AKBA showed potent cytotoxic activity on primary cell cultures of 11 meningiomas at the concentration of 2–8 μM .

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 orthotopic 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.

References:

1. Louis DN, Ohgaki H, Wiestler OD, et al. The 2007 WHO classification of tumours of the central nervous system. *Acta Neuropathol* 2007; 114: 97–109.
2. Krampla W, Newrkla S, Pfisterer W, et al. Frequency and risk factors for meningioma in clinically healthy 75-year-old patients: results of the Transdanube Ageing Study (VITA). *Cancer* 2004; 100: 1208–12.
3. Wöhrer A, Waldhör T, Heinzl H, et al. The Austrian Brain Tumour Registry: a cooperative way to establish a population-based brain tumour registry. *J Neurooncol* 2009; 95: 401–11.
4. Larjaveera S, Haapasalo H, Sankila R, et al. Is the incidence of meningiomas underestimated? A regional survey. *Br J Cancer* 2008; 99: 182–4.
5. Cornelius JF, Slotty PJ, Steiger HJ, et al. Malignant potential of skull base versus non-skull base meningiomas: clinical series of 1,663 cases. *Acta Neurochir (Wien)* 2013; 155: 407–13.
6. Johnson MD, O'Connell M, Facik M, et al. Cerebrospinal fluid stimulates leptomeningeal and meningioma cell proliferation and activation of STAT3. *J Neurooncol* 2012; 107: 121–31.
7. James MF, Han S, Polizzano C, et al. NF2/merlin is a novel negative regulator of mTOR complex 1, and activation of mTORC1 is associated with meningioma and schwannoma growth. *Mol Cell Biol* 2009; 29: 4250–61.
8. Striedinger K, VandenBerg SR, Baia GS, et al. The neurofibromatosis 2 tumor suppressor gene product, merlin, regulates human meningioma cell growth by signaling through YAP. *Neoplasia* 2008; 10: 1204–12.

9. Perry A, Cai DX, Scheithauer BW, et al. Merlin, DAL-1, and progesterone receptor expression in clinicopathologic subsets of meningioma: a correlative immunohistochemical study of 175 cases. *J Neuropathol Exp Neurol* 2000; 59: 872–9.
10. Zhi F, Zhou G, Wang S, et al. A micro-RNA expression signature predicts meningioma recurrence. *Int J Cancer* 2013; 132: 128–36.
11. Falzon G, Pearson S, Murison R, et al. Myelin structure is a key difference in the x-ray scattering signature between meningioma, schwannoma and glioblastoma multiforme. *Phys Med Biol* 2007; 52: 6543–53.
12. Wang X, Gong Y, Wang D, et al. Analysis of gene expression profiling in meningioma: deregulated signaling pathways associated with meningioma and EGFL6 overexpression in benign meningioma tissue and serum. *PLoS One* 2012; 7: e52707.
13. Stuart JE, Lusic EA, Scheck AC, et al. Identification of gene markers associated with aggressive meningioma by filtering across multiple sets of gene expression arrays. *J Neuropathol Exp Neurol* 2011; 70: 1–12.
14. Schroeder T, Czibere A, Zohren F, et al. Meningioma 1 gene is differentially expressed in CD34 positive cells from bone marrow of patients with myelodysplastic syndromes with the highest expression in refractory anemia with excess of blasts and secondary acute myeloid leukemia. *Leuk Lymphoma* 2009; 50: 1043–6.
15. Keller A, Ludwig N, Comtesse N, et al. Combining gene expression signatures and autoantibody profiles in human meningioma. *Gene Ther* 2009; 16: 184–9.
16. Tummalaipalli P, Spomar D, Gondi CS, et al. RNAi-mediated abrogation of cathepsin B and MMP-9 gene expression in a malignant meningioma cell line leads to decreased tumor growth, invasion and angiogenesis. *Int J Oncol* 2007; 31: 1039–50.
17. Zankl H. [The karyotype of the meningioma. Studies on the relations between chromosome set and tumor development (author's transl)]. *Veroff Pathol* 1979; 111: 1–86.
18. James MF, Stivison E, Beauchamp R, et al. Regulation of mTOR complex 2 signaling in neurofibromatosis 2-deficient target cell types. *Mol Cancer Res* 2012; 10: 649–59.
19. Riemenschneider MJ, Perry A, Reifenberger G. Histological classification and molecular genetics of meningiomas. *Lancet Neurol* 2006; 5: 1045–54.
20. Johnson MD, O'Connell M, Vito F, et al. Increased STAT-3 and synchronous activation of Raf-1-MEK-1-MAPK, and phosphatidylinositol 3-Kinase-Akt-mTOR pathways in atypical and anaplastic meningiomas. *J Neurooncol* 2009; 92: 129–36.
21. Barlier A, Graillon T, Defilles C, et al. Strong additive effect of everolimus and octreotide or pasireotide on meningioma cells in vitro: a new therapeutic strategy for these tumors. Abstract: European Society for Medical Oncology meeting, Vienna, Austria, September 28–October 2, 2012; 419PD.
22. Mawrin C, Pachow D, Kirches E. Systemic temsirolimus administration reduces tumor growth in an orthotopic mouse meningioma model. Abstract: European Society for Medical Oncology meeting, Vienna, Austria, September 28–October 2, 2012; 420PD.
23. Brem SS, Bierman PJ, Brem H, et al. National Comprehensive Cancer Network. Central nervous system cancers. *J Natl Compr Canc Netw* 2011; 9: 352–400.
24. Scorsetti M, Alongi F, Clerici E, et al. Temozolomide combined with radiotherapy in the treatment of recurrent cranial meningioma previously treated with multiple surgical resections and two sessions of radiotherapy: a case report and literature review. *Tumori* 2012; 98: 67e–71e.
25. Chamberlain MC. The role of chemotherapy and targeted therapy in the treatment of intracranial meningioma. *Curr Opin Oncol* 2012; 24: 666–71.
26. Kreissl MC, Häscheid H, Löhr M, et al. Combination of peptide receptor radionuclide therapy with fractionated external beam radiotherapy for treatment of advanced symptomatic meningioma. *Radiat Oncol* 2012; 7: 99.
27. Ngwenya LB, Chiocca EA. Do meningioma patients benefit from antiepileptic drug treatment? *World Neurosurg* 2013; 79: 433–4.
28. Pechlivanis I, Wawrzyniak S, Engelhardt M, et al. Evidence level in the treatment of meningioma with focus on the comparison between surgery versus radiotherapy. A review. *J Neurosurg Sci* 2011; 55: 319–28.
29. Moubayed SP, Guertin L, Lambert C, et al. Successful treatment of anaplastic meningioma metastatic to cervical lymph nodes. *Head Neck* 2013; 35: E115–E118.
30. Simó M, Izquierdo C, Bruna J. Systemic treatment of recurrent meningioma. *Eur Assoc NeuroOncol Mag* 2013; 3 (3): 132–8.
31. Grunberg SM, Weiss MH, Russell CA, et al. Long-term administration of mifepristone (RU486): clinical tolerance during extended treatment of meningioma. *Cancer Invest* 2006; 24: 727–33.
32. Chamberlain MC, Glantz MJ, Fadul CE. Recurrent meningioma: salvage therapy with long-acting somatostatin analogue. *Neurology* 2007; 69: 969–73.
33. Pistolesi S, Fontanini G, Boldrini L, et al. The role of somatostatin in vasogenic meningioma associated brain edema. *Tumori* 2003; 89: 136–40.
34. Johnson DR, Kimmel DW, Burch PA, et al. Phase II study of subcutaneous octreotide in adults with recurrent or progressive meningioma and meningeal hemangiopericytoma. *Neuro Oncol* 2011; 13: 530–5.
35. Gama HP, Rocha AJ, Silva CJ, et al. Meningioma growth during interferon beta-1A treatment for multiple sclerosis. *Arq Neuropsiquiatr* 2008; 66: 402–4.
36. Muhr C, Gudjonsson O, Lilja A, et al. Meningioma treated with interferon-alpha, evaluated with [(11)C]-L-methionine positron emission tomography. *Clin Cancer Res* 2001; 7: 2269–76.
37. Bosmans JL, Ysebaert D, De Cock AM, et al. Interferon-alpha and the cure of metastasis of a malignant meningioma in a kidney allograft recipient: a case report. *Transplant Proc* 1997; 29: 838.
38. Zhang ZJ, Muhr C, Wang JL. Interferon-alpha inhibits the DNA synthesis induced by PDGF and EGF in cultured meningioma cells. *Anticancer Res* 1996; 16: 717–23.
39. Zhang ZJ, Wang JL, Muhr C, et al. Synergistic inhibitory effects of interferon-alpha and 5-fluorouracil in meningioma cells in vitro. *Cancer Lett* 1996; 100: 99–105.
40. Wöber-Bingöl C, Wöber C, Marosi C, et al. Interferon-alfa-2b for meningioma. *Lancet* 1995; 345: 331.
41. Koper JW, Zwarthoff EC, Hagemeijer A, et al. Inhibition of the growth of cultured human meningioma cells by recombinant interferon-alpha. *Eur J Cancer* 1991; 27: 416–9.
42. Chamberlain MC. Hydroxyurea for recurrent surgery and radiation refractory high-grade meningioma. *J Neurooncol* 2012; 107: 315–21.
43. Chamberlain MC, Johnston SK. Hydroxyurea for recurrent surgery and radiation refractory meningioma: a retrospective case series. *J Neurooncol* 2011; 104: 765–71.
44. Hahn BM, Schrell UM, Sauer R, et al. Prologed oral hydroxyurea and concurrent 3d-conformal radiation in patients with progressive or recurrent meningioma: results of a pilot study. *J Neurooncol* 2005; 74: 157–65.
45. Fuentes S, Chinot O, Dufour F, et al. [Hydroxyurea treatment for unresectable meningioma]. *Neurochirurgie* 2004; 50: 461–7.
46. Yang SX, Wang YR, Gan HP. [Growth-suppression effect of hydroxyurea on meningioma cells in vitro]. *Zhejiang Da Xue Xue Bao Yi Xue Ban* 2004; 33: 129–32.
47. Paus S, Klockgether T, Urbach H, et al. Meningioma of the optic nerve sheath: treatment with hydroxyurea. *J Neurol Neurosurg Psychiatry* 2003; 74: 1348–50.
48. Giordano F, Savarino A, Pagni CA. Spinal meningioma during hydroxyurea therapy. A paradoxical case report. *Neurolog Sci* 2002; 23: 127–9.
49. Mason WP, Gentili F, Macdonald DR, et al. Stabilization of disease progression by hydroxyurea in patients with recurrent or unresectable meningioma. *J Neurosurg* 2002; 97: 341–6.
50. Newton HB, Slivka MS, Stevens C. Hydroxyurea chemotherapy for unresectable or residual meningioma. *J Neurooncol* 2000; 49: 165–70.
51. Cusimano MD. Hydroxyurea for treatment of meningioma. *J Neurosurg* 1998; 88: 938–9.
52. Schrell UM, Rittig MG, Anders M, et al. Hydroxyurea for treatment of unresectable and recurrent meningiomas. I. Inhibition of primary human meningioma cells in culture and in meningioma transplants by induction of the apoptotic pathway. *J Neurosurg* 1997; 86: 845–52.
53. Chamberlain MC, Tsao-Wei DD, Groshen S. Temozolomide for treatment-resistant recurrent meningioma. *Neurology* 2004; 62: 1210–2.
54. Chamberlain MC, Tsao-Wei DD, Groshen S. Salvage chemotherapy with CPT-11 for recurrent meningioma. *J Neurooncol* 2006; 78: 271–6.
55. Gupta V, Su YS, Samuelson CG, et al. Chemotherapy for meningiomas with Gleevec both in vivo and in vitro. *Neurooncol* 2006; 8: 412.
56. Reardon DA, Norden AD, Desjardins A, et al. Phase II study of Gleevec® plus hydroxyurea (HU) in adults with progressive or recurrent meningioma. *J Neurooncol* 2012; 106: 409–15.
57. Ragel BT, Gillespie DL, Kushnir V, et al. Calcium channel antagonists augment hydroxyurea- and ru486-induced inhibition of meningioma growth in vivo and in vitro. *Neurosurgery* 2006; 59: 1109–21.
58. Preusser M, Spiegl-Kreinecker S, Lötsch D, et al. Trabectedin has promising antineoplastic activity in high-grade meningioma. *Cancer* 2012; 118: 5038–49.
59. Adams EF, Todo T, Schrell UM, et al. Autocrine control of human meningioma proliferation: secretion of platelet-derived growth-factor-like molecules. *Int J Cancer* 1991; 49: 398–402.
60. Birner P, Toumangelova-Uzeir K, Natchev S, et al. STAT3 tyrosine phosphorylation influences survival in glioblastoma. *J Neurooncol* 2010; 100: 339–43.
61. Wernicke AG, Dicker AP, Whiton M, et al. Assessment of Epidermal Growth Factor Receptor (EGFR) expression in human meningioma. *Radiat Oncol* 2010; 5: 46.
62. Caltabiano R, Parisi G, Albanese V, et al. Epidermal growth factor receptor overexpressed malignant fibrous histiocytoma associated with recurrent meningothelial meningioma. *Neurol Med Chir (Tokyo)* 2009; 49: 523–7.
63. Barbieri F, Bajetto A, Porcile C, et al. CXCR receptor and chemokine expression in human meningioma: SDF1/CXCR4 signaling activates ERK1/2 and stimulates meningioma cell proliferation. *Ann NY Acad Sci* 2006; 1090: 332–43.
64. Kuratsu JI, Seto H, Kochi M, et al. Expression of PDGF, PDGF-receptor, EGF-receptor and sex hormone receptors on meningioma. *Acta Neurochir (Wien)* 1994; 131: 289–93.
65. Shamah SM, Alberta JA, Giannobile WV, et al. Detection of activated platelet-derived growth factor receptors in human meningioma. *Cancer Res* 1997; 57: 4141–7.
66. Todo T, Adams EF, Fahlbusch R, et al. Autocrine growth stimulation of human meningioma cells by platelet-derived growth factor. *J Neurosurg* 1996; 84: 852–9.
67. Nakayama Y, Sueishi K, Fukushima T, et al. [Localization of platelet-derived endothelial cell growth factor in human glioblastoma and meningioma]. *Noshuyo Byori* 1994; 11: 187–91.
68. Wen PY, Yung WK, Lamborn KR, et al. Phase II study of imatinib mesylate for recurrent meningiomas (North American Brain Tumor Consortium study 01-08). *Neuro Oncol* 2009; 11: 853–60.
69. Horak P, Wöhrer A, Hassler M, et al. Imatinib mesylate treatment of recurrent meningiomas in preselected patients: a retrospective analysis. *J Neurooncol* 2012; 109: 323–30.
70. Norden AD, Raizer JJ, Abrey LE, et al. Phase II trials of erlotinib or gefitinib in patients with recurrent meningioma. *J Neurooncol* 2010; 96: 211–7.
71. Preusser M, Hassler M, Birner P, et al. Microvascularization and expression of VEGF and its receptors in recurring meningiomas: pathological data in favor of antiangiogenic therapy approaches. *Clin Neuropathol* 2012; 31: 352–60.
72. Puchner MJ, Hans VH, Harati A, et al. Bevacizumab-induced regression of anaplastic meningioma. *Ann Oncol* 2010; 21: 2445–6.
73. Abboud H, Carpentier A, Martin-Duverneuil N, et al. MALT lymphoma presenting as a meningioma. *J Neurooncol* 2005; 75: 221.
74. Schmid S, Aboul-Enein F, Pfisterer W, et al. Vascular endothelial growth factor: the major factor for tumor neovascularization and edema formation in meningioma patients. *Neurosurgery* 2010; 67: 1703–8.
75. Goutagny S, Raymond E, Sterkers O, et al. Radiographic regression of cranial meningioma in a NF2 patient treated by bevacizumab. *Ann Oncol* 2011; 22: 990–1.
76. Lou E, Sumrall AL, Turner S, et al. Bevacizumab therapy for adults with recurrent/progressive meningioma: a retrospective series. *J Neurooncol* 2012; 109: 63–70.
77. Norden AD, Drappatz J, Wen PY. Advances in meningioma therapy. *Curr Neurol Neurosci Rep* 2009; 9: 231–40.
78. Marosi C, Hassler M, Rössler K, et al. Meningioma. *Crit Rev Oncol Hematol* 2008; 67: 153–71.
79. Ragel BT, Couldwell WT, Wurster RD, et al. Chronic suppressive therapy with calcium channel antagonists for refractory meningiomas. *Neurosurg Focus* 2007; 23: E10.
80. Park YS, Lee JH, Harwalkar JA, et al. Acetyl-11-keto-beta-boswellic acid (AKBA) is cytotoxic for meningioma cells and inhibits phosphorylation of the extracellular-signal regulated kinase 1 and 2. *Adv Exp Med Biol* 2002; 507: 387–93.
81. Park YS, Lee JH, Bondar J, et al. Cytotoxic action of acetyl-11-keto-beta-boswellic acid (AKBA) on meningioma cells. *Planta Med* 2002; 68: 397–401.
82. Gehring S, Tapia-Pérez JH, Kirches E, et al. Cytotoxic effects of statins and thiazolidinediones on meningioma cells. *J Neurooncol* 2011; 102: 383–93.
83. Tapia-Pérez JH, Kirches E, Mawrin C, et al. Cytotoxic effect of different statins and thiazolidinediones on malignant glioma cells. *Cancer Chemother Pharmacol* 2011; 67: 1193–201.
84. Bil J, Zapala L, Nowis D, et al. Statins potentiate cytostatic/cytotoxic activity of sorafenib but not sunitinib against tumor cell lines in vitro. *Cancer Lett* 2010; 288: 57–67.
85. Ledezma E, Wittig O, Alonso J, et al. Potentiated cytotoxic effects of statins and ajoene in murine melanoma cells. *Melanoma Res* 2009; 19: 69–74.