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Systemic Treatment of Recurrent Meningioma

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Abstract: Meningioma is the most frequently diagnosed primary brain tumour. Although only a subset of meningioma patients suffer recurrence after standard therapy, these patients require further rescue treatment. Owing to the fact that meningioma over-expresses a great number of potential therapeutic targets, some systemic therapies have been evaluated in recurrent meningioma patients. Cytostatic agents, including combined chemotherapeutic regimens, hydroxyurea and temozolomide, are generally ineffec-

tive. Immunotherapy and hormonal therapy with somatostatin analogues have been suggested as potential therapeutic agents, even though studies have presented contradictory results. Recently, several studies using targeted therapies, such as epidermal growth factor receptor (EGFR), platelet-derived growth factor receptor (PDGFR), and vascular endothelial growth factor (VEGF) inhibitors, showed early promising results. However, additional long-term results are still under evaluation. Furthermore, the combination of vari-

ous medical therapies, such as hydroxyurea and a PDGFR inhibitor, appears to hold some promise. This review provides an overview of the current rationale and evidence base for the various medical therapy approaches tested. **Eur Assoc NeuroOncol Mag 2013; 3 (3): 132–8.**

Key words: meningioma, systemic treatment, chemotherapy, immunotherapy, hormonal therapy, targeted therapies

■ Introduction

Meningioma is the most frequently diagnosed primary brain tumour, accounting for nearly 35.5 % of all primary brain tumours [1]. The prevalence of pathologically confirmed meningioma is estimated to be approximately 97.5/100,000 with an incidence rate of 7.1/100,000/year in the United States [1]. Meningioma is more than twice as common in females than in males (female:male ratio: 2.2:1) and it is also more common in the black population (black:white ratio 1.2:1). Moreover, the incidence increases progressively with age [1].

The majority of meningiomas are classified according to the World Health Organization (WHO) as grade I or so-called benign meningioma (nearly 80 %). They present a prolonged progression-free survival (PFS) and overall survival (OS) (PFS and OS of 90 % at 5 years). In contrast, high-grade meningioma, including atypical or WHO grade II and anaplastic or WHO grade III, differ in important aspects from their benign counterparts [2]. They represent up to 20–35 % of all meningiomas, largely WHO grade II (approximately 20–30 %). WHO grade-III meningioma represents only approximately 2 % of all meningiomas. High-grade meningiomas exhibit an earlier peak incidence, with a small male predominance, and they present a worse PFS (60 % and 30 % at 5 years, for grades II and III, respectively) and OS (80 % and 40 % at 5 years for grades II and III, respectively) [3–5]. Atypical meningiomas carry a 7–8-fold increased risk of recurrence and about a 2-fold increased risk of death at 3–5 years compared to benign meningioma [3, 6].

Although there are scarce data regarding meningioma aetiology, 2 risk factors, ionizing radiation and genetic predisposition [7], have been described. Genetic aberrations such as focal chromosomal deletion of the NF2 (type-2 neurofibroma-

tosis) gene on chromosome 22 and other more complex genetic changes have been associated with sporadic meningioma. Moreover, the complexity of genetic aberrations clearly increases with tumour grade [8].

Meningioma results from a clonal outgrowth derived from arachnoid cap cells and it presents some differential facts compared to other brain tumours. First, the natural history of meningioma is relatively unknown. This is due to the fact that meningioma has a prevalence of nearly 3 % of subclinical disease as suggested by autopsy studies, and it is frequently discovered incidentally, introducing a detection bias [8]. Second, research regarding the molecular pathogenesis has been limited in comparison to gliomas. All these disadvantages, together with a lack of data from prospective series, make meningioma research a challenging area of study.

Standard therapy for meningioma includes extensive surgical resection for grade I followed by radiation therapy at front line for high-grade meningioma and at recurrence for grade I [9]. Although radiation therapy following surgical resection is the standard and recommended therapy for high-grade meningioma, there is still some controversy among studies [9]. Two currently ongoing phase-II trials (RTOG-0539, EORTC 22042-26042) are expected to provide better evidence to define optimal therapy in high-grade meningioma patients. Recurrence after completion of both therapies is managed by re-resection or re-irradiation when feasible [10, 11]. Unfortunately, there is no well-established treatment for meningioma patients with a good performance status who suffer recurrence after completion of these therapies. However, meningiomas have some particularities that make them susceptible and potential good candidates to respond to systemic therapies. The tumour is located outside the blood-brain barrier, it presents high vascularity supply, and it over-expresses a variety of potential therapeutic targets, including growth factors and their receptors, such as PDGF, EGF, and IGF, angiogenesis factors such as VEGF and VEGF receptor, and hormonal receptors such as oestrogen, progesterone, androgen, growth hormone, and somatostatin receptors. In this setting, several approaches have been assessed, although most of them have yielded disappointing results [12]. Nevertheless, 3 of these tested systemic treatments – hydroxyurea, alpha-interferon, and somatostatin analogue – are recommended for the treat-

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ment of recurrent meningioma by the Central Nervous System National Comprehensive Cancer Network (CNS NCCN, 2012) guidelines [13].

The aim of the present review is to provide an up-to-date survey of the advances of systemic treatments in recurrent meningioma patients.

■ Systemic Therapies

Several systemic therapies have been evaluated in recurrent meningioma patients, especially over the last 10 years. The systemic treatment attempts may be grouped according to the mechanism of action and the targets of the drug or combination of drugs assessed. The most relevant clinical trials are summarized in Table 1.

Chemotherapy

Treatment strategy using classic systemic cytostatic drugs has been based on 3 different approaches. First, the drugs and the chemotherapy schedules tested were selected according to the activity and the results obtained in experimental studies. Secondly, assuming that a meningioma has histopathogenic similarities with soft-tissue sarcomas, combined chemotherapeutic regimens used in these patients were reproduced in meningiomas. Lastly, chemotherapy regimens normally employed in glioma treatment have also been explored. Unfortunately, the antineoplastic agents studied, presented very limited results [26–29].

The first evidence from testing chemotherapy in recurrent meningioma came from combined chemotherapeutic regimens, including ifosfamide and mesna [27], cisplatin and doxorubicin [26], cyclophosphamide, adriamycin, and vincristine (CAV [28]), and, more recently, high-dose chemotherapy (carboplatin, etoposide, and thiothepa) followed by haematopoietic stem cells [29]. These case reports and small clinical series yielded disappointing results [26–29]. Cham-

berlain et al treated 14 WHO grade-III meningioma patients with CAV therapy just 2–4 weeks after adjuvant radiotherapy. Despite a substantial survival benefit of a median of 4 years, the authors suggested that this benefit was more related to the effects of radiotherapy than chemotherapy itself [28].

On the other hand, hydroxyurea (HU) is an antineoplastic drug that has demonstrated potent inhibition of cultured meningioma cells by inducing apoptosis *in vitro* [29]. The first phase-II trial with 4 recurrent meningioma patients resulted in prolonged disease-free survival (PFS at 6 months [PFS6] 100 %) with a 50-% partial radiographic response [14]. After these promising preliminary results, several subsequent phase-II clinical trials in recurrent meningioma patients suggested modest efficacy with an acceptable toxicity profile. The interval of PFS6 in these studies was 13–77 months [30–36]. The most important limitation of these studies is that patients were neither previously treated with radiotherapy nor were the drugs administered concomitantly [30–36]. Conversely, a large retrospective case series study with recurrent grade-I and high-grade meningioma treated with HU after surgery and radiotherapy demonstrated a median PFS of 2 months with no radiographic responses [15, 16]. In 2012, a phase-II trial combining HU with imatinib, a PDGF inhibitor, was published [17]. Recurrent grade-I and high-grade meningioma patients were included. Although there were no radiographic responses, median PFS was 7 months (14 and 5.3 months for grade-I and high-grade meningioma, respectively) and median OS was 5.5 and 1.5 years for grade-I and high-grade meningioma, respectively. Thus, although these results are modest and not directly comparable, combined treatment seems better in terms of PFS and OS compared to the studies with HU alone. In addition, another phase-II trial combining HU with verapamil, a calcium channel antagonist, is ongoing (Table 2). Calcium channel antagonists block the stimulatory growth effects by inhibiting calcium-dependent secondary messenger pathways of multiple growth factors, and it has been demonstrated that they increase the inhibitory growth

Table 1. Summary of the most relevant medical therapies tested in recurrent meningioma patients previously treated with surgery and radiotherapy.

Drug	Study design	n	WHO grade (n grade I/n high grade)	PFS (months)	PFS (%)	OS (years)	RRR (%)	Best RR (%)
Hydroxyurea [14]	Phase II	4	3/1	nr	100	nr	75	nr
Hydroxyurea [15]	Retrospective	60	60/0	2	10	nr	0	SD 35
Hydroxyurea [16]	Retrospective	35	0/35	2	3	nr	0	SD 43
Hydroxyurea and imatinib [17]	Phase II	21	8/13	7	62	5.5	0	SD 67
CPT-11 [18]	Phase II	16	16/0	5	0	nr	0	SD 81
Mifepristone [19]	Phase III	160	160/0	10	nr	nr	2	nr
Interferon- α [20]	Phase II	35	35/0	7	54	0.7	0	SD 74
Octeotride [21]	Phase II	16	8/8	5	44	0.6	31	PR 31
Octeotride [22]	Phase II	12	3/9	4	17	2.7	0	SD 75
Imatinib [23]	Retrospective	9	1/8	16	67	3.5	0	SD 78
Bevacizumab [24]	Retrospective	15	0/15	6.5	44	1.3	0	SD 87
Bevacizumab and chemotherapy [25]	Retrospective	14	6/8	18	86	nr	7	SD 79

WHO: World Health Organization; PFS: median progression-free survival; PFS6: progression-free survival rate at 6 months; OS: median overall survival; RRR: rate of radiographic response; Best RR: best radiographic response; nr: not reported; SD: stable disease; PR: partial response

Table 2. Summary of the most relevant ongoing trials in recurrent meningioma patients. Source: clinicaltrials.gov

Agent	Study	Mechanism of action	Site
Hydroxyurea	Phase II	Ribonucleotide reductase inhibitor	UNICANCER
Hydroxyurea plus verapamil	Phase II	Ribonucleotide reductase inhibitor Calcium channel antagonist	University of Utah
Interferon- α	Phase II	Antiproliferative and antiangiogenic activity	M.D. Anderson Cancer Center
Pasireotide (SOM230B/SOM230C)	Phase II	Somatostatin analogue	University of Utah
Erlotinib	Phase I, II	EGFR inhibitor	National Cancer Institute
Gefinitib	Phase II	EGFR inhibitor	Sidney Kimmel Comprehensive Cancer Center
Sunitinib	Phase II	VEGFR and PDGFR inhibitors	Memorial Sloan-Kettering Cancer Center University Magdeburg
Imatinib mesylate	Phase II	PDGFR inhibitor	National Cancer Institute
Imatinib mesylate	Phase II	PDGFR inhibitor	
Hydroxyurea		Ribonucleotide reductase inhibitor	Istituto Scientifico H. San Raffael
Valatanib	Phase II	VEGFR and PDGFR inhibitors	Northwestern University
Bevacizumab	Phase II	VEGF antibody	Sarah Cannon Research Institute
Everolimus		mTOR inhibitor	
Bevacizumab	Phase II	VEGF antibody	Northwestern University M.D. Anderson Cancer Center
Ispinesib	Phase I	Inhibitor of kinesin spindle protein	National Cancer Institute
Antineoplastona	Phase II	Modulates ras oncogene, gene P53	Burzynski Research Institute

EGFR: epidermal growth factor receptor; VEGFR: vascular endothelial growth factor receptor; PDGFR: platelet-derived growth factor receptor

effects of HU in experimental studies [37]. Lastly, several drugs that are able to cross the blood-brain barrier have also been tested. Temozolomide, an alkylating agent that reacts with DNA bases and represents the current antineoplastic cornerstone drug in high-grade glioma treatment, did not demonstrate efficacy against meningioma in a phase-II trial (median PFS 5 months) [38]. This result may be explained by the high levels of activity in meningioma cells of O6-methylguanine-DNA-methyltransferase, the DNA repair enzyme responsible for creating a resistant phenotype to alkylating agents [39, 40]. Similarly, other drugs have been tested with disappointing results. Irinotecan, which also demonstrated activity against meningioma cells in preclinical studies, proved ineffective in a phase-II trial in WHO grade-I recurrent meningioma patients (median PFS 5 months) [18, 41]. Finally, cytosine arabinoside did not show any effect in a single case study [42].

The resistance of meningioma to chemotherapy, in a tumour with high vascularity supply and located outside the blood-brain barrier, is not entirely understood. A high but heterogeneous expression of drug resistance-associated proteins, such as p-glycoprotein, multidrug resistance-associated protein, lung resistance-related protein, metallothionein, and topoisomerase II alpha, has been observed in all grades of meningioma specimens, and it has been suggested as the main factor explaining this extreme profile of drug resistance to chemotherapy [43]. These proteins are expressed especially in the endothelium and they may confer an impaired penetration of therapeutic agents through the blood-tumour barrier [44].

In summary, all cytostatic-agent studies in recurrent meningioma patients have proved ineffective. Preliminary hydroxyurea phase-II and case series studies obtained the most promising results. However, this benefit has not been demonstrated

in further studies. The combination of hydroxyurea and imatinib showed the best results in a well-designed phase-II trial.

Immunotherapy

Interferon- α (IFN- α) is a biologic agent with efficacy in a variety of systemic malignancies due to its antiproliferative and antiangiogenic activity [45]. Moreover, preclinical studies have documented that IFN- α inhibits the growth of cultured human meningioma cell lines [46]. Based on this rationale, small clinical studies using IFN- α in patients with recurrent meningioma were conducted, resulting in promisingly long stabilization periods [47, 48]. Hence, in 2008, Chamberlain et al conducted a phase-II trial in grade-I recurrent meningioma patients treated with IFN- α administered subcutaneously every other day. This resulted in moderate toxicity but with promising outcome results. Median PFS was 7 months and PFS6 was 54 %. However, no patients presented a radiographic response and stable disease was the best response in 74 % of patients. Thus, this study demonstrated moderate but noteworthy results in grade-I recurrent meningioma patients [20]. Nevertheless, as mentioned above, due to the unknown natural history of meningioma, especially the growth ratio of recurrent meningiomas, these results have to be interpreted with caution.

Hormonal Therapy

Progesterone receptors (PR) are more frequently expressed in grade-I meningioma (in nearly 80 %) and their presence diminishes with higher histological grade. Likewise, the PR status has been associated with specific gene expression located on the long arm of chromosome 22 near the NF2 gene [49]. This means that meningioma patients with a positive PR status have significant up-regulation of these genes and patients with negative PR status are more likely to have a 22q loss [49]. In this setting, several studies have evaluated the efficacy of

the anti-progesterone agent mifepristone (RU486) in recurrent meningioma patients. Although initial small phase-II trials showed promising results, a further phase-III trial in WHO grade-I recurrent meningioma patients failed to demonstrate any benefit (PFS was 10 months in the treatment arm vs 12 months in the placebo arm) with no radiographical responses [19, 50–52]. In contrast, a recent phase-II trial using mifepristone in recurrent meningioma patients (most of them grade I) demonstrated a minor radiographic response in 29 % of patients [53].

Recently, there has been particular interest in the potential therapeutic action of somatostatin (SST) analogues. SST is a neuropeptide that plays an important role in several relevant cancer pathways, such as the inhibition of angiogenesis and tumour invasion, and in the induction of apoptosis [54]. SST receptors are composed of 5 subtypes of receptors (sstr1–5). Meningiomas show a high frequency of SST receptor expression (nearly 90 %), most frequently of the sstr2a subtype, but their functional role remains unclear [55]. Due to the short half-life of SST, a number of SST analogues with longer half-lives have been developed. A prototype of a long-acting SST analogue agonist, with a clear preference for sstr2a, is octreotide. Since 2007, there have been anecdotal reports of octreotide improving meningioma-related signs and symptoms with no radiographic improvement [56–58]. Recently, 3 phase-II trials yielded contradictory results in terms of radiographic responses [21, 22, 59]. A first trial using sustained-release intramuscular SST administered monthly in 16 patients with recurrent grade-I and high-grade meningioma showed a median PFS of 5 months (PFS6 44 %). Moreover, partial radiographic response was found in 31 % [21]. The second phase-II trial, using daily subcutaneous octreotide, treated 11 patients with recurrent grade-I and high-grade meningioma and found a median PFS of 4.2 months (PFS6 33 %) with no radiographic response [22]. Lastly, a phase-II trial exclusively performed in recurrent high-grade meningioma patients using sustained-release intramuscular SST demonstrated a median PFS of 4 months (PFS6 43 %) with no radiographic response [59]. In addition, pasireotide, a novel SST analogue with a wider SST receptor spectrum (including subtypes 1, 2, 3, and 5) and greater affinity (particularly for subtypes 1, 3, and 5), has been developed [60]. However, preliminary results of a phase-II trial, using long-acting pasireotide LAR in 26 patients with recurrent grade-I and high-grade meningioma, did not show promising results, yielding a median PFS of 5 months (PFS6 29 %) [61].

Targeted Molecular Agents

Targeted molecular agents are drugs that block some of the cell signalling pathways involved in neoplastic transformation by interfering with specific targeted molecules needed for carcinogenesis. Our understanding of brain tumour biology and recognition of the importance of the dysregulation of cell signalling pathways as a cause of neoplastic transformation have grown in recent years. In contrast to the extensive research on glioma, little is known about meningioma biology [62–65]. Preclinical studies have identified aberrant expression of critical signalling molecules in meningioma cells [66, 67]. Based on this approach, several studies using targeted molecular agents have recently been performed in recurrent

meningioma patients. These trials have been classified into 5 groups depending on their main target: (1) cellular signal transduction tyrosine kinases, (2) intracellular signalling kinases, (3) tumour vasculature, (4) other molecular targets, and (5) multitargeted or combined therapies [68].

Tyrosine kinase inhibitors are drugs against tyrosine kinases or their receptors. Tyrosine kinases are a group of protein kinases that are critical to many cellular signal transduction pathways involved in cell proliferation, growth, survival, adhesion, motility, and differentiation [69]. In addition, receptor tyrosine kinases are transmembrane proteins containing an extracellular binding domain and an intracellular kinase domain that activates intracellular signalling pathways. This group includes the epidermal growth factor receptor (EGFR) and the platelet-derived growth factor receptor (PDGFR).

The EGFR is over-expressed in > 60 % of meningiomas and studies *in vitro* have demonstrated that EGF and TGF- α activate these receptors, thereby stimulating meningioma growth [44, 63, 70–75]. Recently, 2 phase-II trials with 2 EGFR inhibitors, erlotinib and gefitinib, in recurrent grade-I and high-grade meningioma patients did not find any objective radiographic responses. Median PFS of the analysis of pooled data in both studies was 2.5 months with a PFS6 rate of 25 % for grade-I and 29 % for high-grade meningioma, respectively. These studies concluded that neither gefitinib nor erlotinib alone appeared to have a significant activity against recurrent meningioma [76].

In addition, most meningiomas also express PDGF and PDGF receptor [77–80]. PDGFR is a fundamental driver of cell proliferation in many tumours, thus supporting meningioma cell growth and maintenance. Expression levels of both PDGF and PDGFR are higher in atypical and malignant meningiomas than in benign meningiomas [78]. Moreover, meningioma cell culture studies provide evidence that the administration of PDGF results in the stimulation of tumour growth and activation of intracellular signalling kinases, while proliferation of meningioma cells can be inhibited by anti-PDGF antibodies [81–83]. The first phase-II study with a PDGFR inhibitor, imatinib mesylate, conducted in grade-I and high-grade recurrent meningioma patients, did not show any radiographic response. Median PFS was 2 months and the PFS6 rate was 29 % (45 % for grade I but 0 % for high grade); there was, therefore, minimal activity against recurrent meningiomas [84]. Conversely, a recent retrospective study conducted in preselected recurrent grade-I and high-grade meningioma patients with positive immunohistochemical PDGFR staining confirmation and treated with imatinib showed promising results. Although no complete or even partial radiographic response was observed, median PFS was 16 months with a PFS6 rate of 67 % [23].

The second group of targeted therapies includes drugs that interact with intracellular kinases, a family of enzymes involved in the phosphorylation of serine and threonine residues of their substrates. Many of these kinases serve as intermediaries in important signalling pathways. This group includes phosphatidylinositol 3-kinase/AKT PI3k/Akt inhibitors, ras-mitogen-activated protein kinase (MAPK) inhibitors and protein kinase C inhibitors. MAPK and PI3k/Akt path-

way have been demonstrated to play a role in signal transduction in meningioma, especially in benign meningioma [82, 85–87]. However, no clinical studies have been reported with drugs concerning these intracellular signalling kinases in meningioma patients.

The third group of targeted therapies is related to tumour angiogenesis. This process is critical for the growth of many solid tumours and meningiomas, which are highly vascular tumours that derive their blood supply predominantly from meningeal vessels [88]. Thus, the inhibition of angiogenesis is a potentially important approach in treating meningioma patients. Vascular endothelial growth factor (VEGF) plays a central role in tumour angiogenesis, and there is increasing evidence that inhibition of soluble VEGF or VEGFR can lead to significant anti-tumour effects [89, 90]. VEGF and VEGFR are expressed in meningiomas and the level of expression increases with the tumour grade [91–93]. VEGF expression is 2-fold increased in atypical meningiomas and 10-fold in malignant meningiomas compared to benign meningiomas [91]. After the first case report of partial remission of a high-grade recurrent meningioma induced by anti-angiogenic therapy, 2 clinical studies using bevacizumab were reported on in 2012 [24, 25, 94]. Bevacizumab is a monoclonal antibody that inhibits VEGF with demonstrated activity in other systemic cancers as well as in glioblastoma [89, 90, 95]. A retrospective case series study of high-grade recurrent meningioma patients treated with bevacizumab demonstrated a median PFS of 6.5 months with a PFS6 rate of 44 %. However, no complete or partial radiographic responses were observed, although minor response was documented in 2 patients. In terms of toxicity, bevacizumab was relatively well-tolerated although 3 patients (20 %) developed non-fatal intratumoural haemorrhage. These results suggest that bevacizumab may be an effective therapeutic approach for high-grade recurrent meningioma patients [24]. The second retrospective case series study in recurrent meningioma patients reported this year also supported the use of bevacizumab for this indication [25]. In this study, patients received bevacizumab alone ($n = 4$) or combined with chemotherapy ($n = 10$), including etoposide- ($n = 6$) or temozolomide-based regimens ($n = 4$), and demonstrated a median PFS of 17.9 months with a PFS6 rate of 85.7 %. However, no complete radiographic responses were observed, although one patient treated with bevacizumab and etoposide presented partial response. Despite these promising results, this study has some limitations. It was retrospective in nature and the majority of patients received chemotherapy plus bevacizumab.

Following this line, the multitargeted agents sunitinib and vatalanib, which inhibit several kinases such as VEGFR and PDGFR, have demonstrated strong cytostatic and anti-migratory effects on human meningioma cells [96]. To date, preliminary results have been published for 2 phase-II trials. The first study included mostly recurrent high-grade meningioma patients treated with sunitinib. This study showed a median PFS of 4.6 months with a PFS6 rate of 36 %, with one patient demonstrating partial radiographic response. However, patients presented important toxicities (34 events of grade-3–4 toxicity) [97]. The other phase-II trial tested vatalanib in high-grade recurrent meningioma patients and observed a median PFS of 3.7 months with a PFS6 rate of 37.5 %. However, one

patient presented a partial response, and vatalanib seems to have been better tolerated (10 events of grade-3–4 toxicity) than sunitinib [98].

Finally, other therapies designed to act on new molecular targets involved in tumourigenesis such as IGFR, histone deacetylases, ubiquitin-proteasome system, heat shock proteins, cytokines like TGF- β , and DNA repair proteins have not been evaluated in recurrent meningioma patients so far although one recent report has documented a response in an incidental meningioma of a patient treated with chemotherapy combined with an IGFR inhibitor [99].

■ Conclusions

Recurrent meningioma patients are a relevant although not very large group of patients who have made recourse to surgery, radiation therapy, and even to radiosurgery. Therefore, these patients require further treatment options. In this setting, systemic drugs have a potential role in the therapeutic armamentarium. Up to now, most studies have shown disappointing or limited results with only one drug tested in phase-III trials.

Clinical trials in meningioma have several unresolved problems, making it difficult to draw clear conclusions. One limitation is the heterogeneity of the patients included. Almost all studies assumed that the behaviour of recurrent grade-I meningiomas was similar to grade II or III, though in fact the natural history and the growth rate of untreated meningioma is unknown. This point becomes crucial when the endpoint of the phase-II trial is PFS or the PFS6 rate or when a biological agent is tested, the main action of which is the slowing down or blocking of tumour growth. Thus, based on this background, the radiological response rate would be a more reliable endpoint than PFS.

Alternatively, the use of comparative randomized phase-II designs may be in order. Actually, the control group of the only phase-III study published showed a better PFS than the most promising phase-II studies. However, the details of this study are scarce because it has only been reported in a congress abstract. Moreover, data provided by retrospective studies are not useful as screening proof, because PFSs of phase-II studies are clearly worse than the inevitably biased retrospective studies.

Even though several studies have provided in recent years better understanding of the molecular characteristics of meningioma, identifying novel targets for therapy, researching molecular pathogenesis, and learning about the critical molecular changes driving tumour growth need to be addressed if we want to increase the likelihood of success of either single or combined drug selection.

In conclusion, although systemic therapy research on recurrent meningioma patients has substantially increased over the last years, further basic and clinical research is needed to clearly elucidate the most effective systemic therapy options for recurrent meningioma patients.

■ Conflict of Interest

The authors state that no conflict of interests exists.

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References:

- Dolecek TA, Propp JM, Stroup NE, et al. CBTRUS Statistical Report: Primary brain and central nervous system tumors diagnosed in the United States in 2005–2009. *Neuro Oncol* 2012; 14 (Suppl 5): v1–v49.
- Rogers L, Gilbert M, Vogelbaum MA. Intracranial meningiomas of atypical (WHO grade II) histology. *J Neurooncol* 2010; 99: 393–405.
- Perry A. Meningiomas. In: McLendon R, Rosenblum M, Bigner DD (eds). *Russell & Rubinstein's Pathology of Tumors of the Nervous System*. Arnold, London, 2006; 427–74.
- Louis DN, Ohgaki H, Wiestler OD, et al (eds). *World Health Organization classification of tumours of the central nervous system*. 4th ed. IARC, Lyon, 2007.
- Bruna J, Brell M, Ferrer I, et al. Ki-67 proliferative index predicts clinical outcome in patients with atypical or anaplastic meningioma. *Neuropathology* 2007; 27: 114–20.
- Perry A. Unmasking the secrets of meningioma: a slow but rewarding journey. *Surg Neurol* 2004; 61: 171–3.
- Riemenschneider MJ, Perry A, Reifenberger G. Histological classification and molecular genetics of meningiomas. *Lancet Neurol* 2006; 5: 1045–54.
- Wiemels J, Wrensch M, Claus EB. Epidemiology and etiology of meningioma. *J Neurooncol* 2010; 99: 307–14.
- Rogers L, Gilbert M, Vogelbaum MA. Intracranial meningiomas of atypical (WHO grade II) histology. *J Neurooncol* 2010; 99: 393–405.
- Sughrue ME, Sanai N, Shangari G, et al. Outcome and survival following primary and repeat surgery for World Health Organization Grade III meningiomas. *J Neurosurg* 2010; 113: 202–9.
- Kano H, Takahashi JA, Katsuki T, et al. Stereotactic radiosurgery for atypical and anaplastic meningiomas. *J Neurooncol* 2007; 84: 41–7.
- Wen PY, Quant E, Drappatz J, et al. Medical therapies for meningiomas. *J Neurooncol* 2010; 99: 365–78.
- Brem SS, Bierman PJ, Brem H, et al. Central nervous system cancers. *J Natl Compr Canc Netw* 2011; 9: 352–400.
- Schrell UM, Rittig MG, Anders M, et al. Hydroxyurea for treatment of unresectable and recurrent meningiomas II. Decrease in the size of meningiomas in patients treated with hydroxyurea. *J Neurosurg* 1997; 86: 840–4.
- Chamberlain MC, Johnston SK. Hydroxyurea for recurrent surgery and radiation refractory meningioma: a retrospective case series. *J Neurooncology* 2011; 104: 765–71.
- Chamberlain MC. Hydroxyurea for recurrent surgery and radiation refractory high-grade meningioma. *J Neurooncol* 2012; 107: 315–21.
- 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.
- Chamberlain MC, Tsao-Wei DD, Groshen S. Salvage chemotherapy with CPT-11 for recurrent meningioma. *J Neurooncol* 2006; 78: 271–6.
- Grunberg SM, Rankin C, Townsend J, et al. Phase III double-blind randomized placebo-controlled study of mifepristone (RU) for the treatment of unresectable meningioma. *Proc Am Soc Clin Oncol* 2001; 20: A222.
- Chamberlain MC, Glantz MJ. Interferon-alpha for recurrent World Health Organization grade 1 intracranial meningiomas. *Cancer* 2008; 113: 2146–51.
- Chamberlain MC, Glantz MJ, Fadul CE. Recurrent meningioma: salvage therapy with long-acting somatostatin analogue. *Neurology* 2007; 69: 969–73.
- 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.
- 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.
- Nayak L, Iwamoto FM, Rudnick JD, et al. Atypical and anaplastic meningiomas treated with bevacizumab. *J Neurooncol* 2012; 109: 187–93.
- 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.
- Stewart DJ, Dahrrouge S, Wee M, et al. Intraarterial cisplatin plus intravenous doxorubicin for inoperable recurrent meningiomas. *J Neurooncol* 1995; 24: 189–94.
- Kyritsis AP. Chemotherapy for meningiomas. *J Neurooncol* 1996; 29: 269–72.
- Chamberlain MC. Adjuvant combined modality therapy for malignant meningiomas. *J Neurosurg* 1996; 84: 733–6.
- Rosenfeld A, Kletzel M, Duerst R, et al. A phase II prospective study of sequential mifepristone plus hydroxyurea with hematopoietic stem cell rescue for the treatment of selected high risk and recurrent central nervous system tumors. *J Neurooncol* 2010; 97: 247–55.
- Newton HB, Slivka MA, Stevens C. Hydroxyurea chemotherapy for unresectable or residual meningioma. *J Neurooncol* 2000; 49: 165–70.
- Newton HB, Scott SR, Volpi C. Hydroxyurea chemotherapy for meningiomas: enlarged cohort with extended follow-up. *J Neurosurg* 2004; 18: 495–9.
- Mason WP, Gentili F, Abrey LF, et al. Stabilization of disease progression by hydroxyurea in patients with recurrent or unresectable meningioma. *J Neurosurg* 2002; 97: 341–6.
- Rosenthal M, Ashley D, Cher L. Treatment of high risk or recurrent meningiomas with hydroxyurea. *J Clin Neurosci* 2002; 9: 156–8.
- Hahn BM, Schrell UM, Sauer R, et al. Prolonged 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.
- Loven D, Harhoff R, Sever ZB, et al. Non-resectable slow-growing meningiomas treated by hydroxyurea. *J Neurooncol* 2004; 67: 221–6.
- Kim M, Yu D, Jung Y, et al. Long-term follow-up result of hydroxyurea chemotherapy for recurrent meningiomas. *J Korean Neurosurg Soc* 2012; 52: 517–22.
- Ragel BT, Couldwell WT, Wurster RD, et al. Chronic suppressive therapy with calcium channel antagonists for refractory meningiomas. *Neurosurg Focus* 2007; 23: E10.
- Chamberlain MC, Tsao-Wei D, Groshen S. Temozolomide for treatment-resistant recurrent meningioma. *Neurology* 2004; 62: 1210–2.
- Hegi ME, Diserens AC, Gorlia T, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. *N Engl J Med* 2005; 352: 997–1003.
- De Robles P, McIntyre J, Kalra S, et al. Methylation status of MGMT gene promoter in meningiomas. *Cancer Genet Cytogenet* 2008; 187: 25–7.
- Gupta V, Su YS, Samuelson CG, et al. Irinotecan: a potential new chemotherapeutic agent for atypical or malignant meningiomas. *J Neurosurg* 2007; 106: 455–62.
- Benesch M, Siegler N, Hoff K, et al. Safety and toxicity of intrathecal liposomal cytarabine (Depocyte) in children and adolescents with recurrent or refractory brain tumors: a multi-institutional retrospective study. *Anticancer Drugs* 2009; 20: 794–9.
- Haroun RI, Clatterbuck RE, Gibbons MC, et al. Extreme drug resistance in primary brain tumors: in vitro analysis of 64 resection specimens. *J Neurooncol* 2002; 58: 115–23.
- Andersson U, Malmer B, Bergenheim AT, et al. Heterogeneity in the expression of markers for drug resistance in brain tumors. *Clin Neuropathol* 2004; 23: 21–7.
- Von Marschall Z, Scholz A, Cramer T, et al. Effects of interferon alpha on vascular endothelial growth factor gene transcription and tumor angiogenesis. *J Natl Cancer Inst* 2003; 95: 437–48.
- Koper JW, Zwarthoff EC, Hagemeyer A, et al. Inhibition of the growth of cultured human meningioma cells by recombinant interferon-alpha. *Eur J Cancer* 1991; 27: 416–9.
- Kaba SE, DeMonte F, Bruner JM, et al. The treatment of recurrent unresectable and malignant meningiomas with interferon-alpha-2B. *Neurosurgery* 1997; 40: 271–5.
- Muhr C, Gudjonsson O, Lilja A. Meningioma treated with interferon-alpha, evaluated with methionine-PET. *Clin Cancer Res* 2001; 7: 2269–76.
- Claus EB, Park PJ, Carroll R, et al. Specific genes expressed in association with progesterone receptors in meningioma. *Cancer Res* 2008; 68: 314–22.
- Haak HR, de Keizer RJ, Hagenouw-Taal JC, et al. Successful mifepristone treatment of recurrent, inoperable meningioma. *Lancet* 1990; 336: 124–5.
- Grunberg SM, Weiss MH, Spitz IM, et al. Treatment of unresectable meningiomas with the antiprogesterone agent mifepristone. *J Neurosurg* 1991; 74: 861–6.
- Lamberts SW, Tanghe HL, Avezaat CJ, et al. Mifepristone (RU 486) treatment of meningiomas. *J Neurol Neurosurg Psychiatry* 1992; 55: 486–90.
- 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.
- Pyronnet S, Boussquet C, Najib S, et al. Antitumor effects of somatostatin. *Mol Cell Endocrinol* 2008; 286: 230–7.
- Arena S, Barbieri F, Thellung S, et al. Expression of somatostatin receptor mRNA in human meningiomas and their implication in vitro antiproliferative activity. *J Neurooncol* 2004; 66: 155–66.
- García-Luna PP, Relimpio F, Pumar A, et al. Clinical use of octreotide in unresectable meningiomas. A report of three cases. *J Neurosurg Sci* 1993; 37: 237–41.
- Runzi MW, Jaspers C, Windeck R, et al. Treatment of meningioma with octreotide. *Lancet* 1989; 2: 217–8.
- Jaffrain-Rea ML, Minniti G, Santoro A, et al. Visual improvement during octreotide therapy in a case of epissellar meningioma. *Clin Neurol Neurosurg* 1998; 100: 40–3.
- Simó M, Macià M, Plans G, et al. Recurrent high grade meningioma: Phase II trial with somatostatin analogue therapy. *Neuro Oncol* 2012; 14 (Suppl 3): 75.
- Bruns C, Lewis I, Briner U, et al. SOM230: a novel somatostatin peptidomimetic with broad somatotropin release inhibiting factor (SRIF) receptor binding and a unique antisecretory profile. *Eur J Endocrinol* 2002; 146: 707–16.
- Norden AD, Hammond S, Drappatz J, et al. Phase II study of monthly pasireotide LAR (SOM 230C) for recurrent or progressive meningioma. *J Clin Oncol* 2011; 29: 2040.
- McMullen KP, Stieber VW. Meningioma: current treatment options and future directions. *Curr Treat Options Oncol* 2004; 5: 499–509.
- Johnson M, Toms S. Mitogenic signal transduction pathways in meningiomas: novel targets for meningioma chemotherapy? *J Neuropathol Exp Neurol* 2005; 64: 1029–36.
- Jagannathan J, Oskouian RJ, Yeoh HK, et al. Molecular biology of unresectable meningiomas: implications for new treatments and review of the literature. *Skull Base* 2008; 18: 173–87.
- Ragel B, Jensen RL. New approaches for the treatment of refractory meningiomas. *Cancer Control* 2003; 10: 148–58.
- Johnson MD, Sade B, Milano MT, et al. New prospects for management and treatment of inoperable and recurrent skull base meningiomas. *Neurooncol* 2008; 86: 109–22.
- Simon M, Boström JP, Hartmann C. Molecular genetics of meningiomas: from basic research to potential clinical applications. *Neurosurgery* 2007; 60: 787–98.
- Wen PY, Quant E, Drappatz J, et al. Medical therapies for meningiomas. *J Neurooncol* 2010; 99: 365–78.
- Campbell BA, Jhamb A, Maguire JA, et al. Meningiomas in 2009: controversies and future challenges. *Am J Clin Oncol* 2009; 32: 73–85.
- Weisman AS, Raguet SS, Kelly PA. Characterization of the epidermal growth factor receptor in human meningioma. *Cancer Res* 1987; 47: 2172–6.
- Carroll RS, Black PM, Zhang J, et al. Expression and activation of epidermal growth factor receptors in meningiomas. *J Neurosurg* 1997; 87: 315–23.
- Jones NR, Rossi ML, Gregoriou M, et al. Epidermal growth factor receptor expression in 72 meningiomas. *Cancer* 2010; 66: 152–5.
- Johnson MD, Horiba M, Winnier AR, et al. The epidermal growth factor receptor is associated with phospholipase C-gamma 1 in meningiomas. *Hum Pathol* 1994; 25: 146–53.
- Sanfilippo JS, Rao CV, Guarnaschelli JJ, et al. Detection of epidermal growth factor and transforming growth factor alpha protein in meningiomas and other tumors of the central nervous system in human beings. *Surg Gynecol Obstet* 1993; 177: 488–96.
- Linggood RM, Hsu DW, Efrid JT, et al. TGF alpha expression in meningioma – tumor progression and therapeutic response. *J Neurooncol* 1995; 26: 45–51.
- Norden AD, Raizer JJ, Abrey LE. Phase II trials of erlotinib or gefitinib in patients with

- recurrent meningioma. *J Neurooncol* 2010; 96: 211–7.
77. Wang JL, Nistér M, Hermansson M, et al. Expression of PDGF beta-receptors in human meningioma cells. *Int J Cancer* 1990; 46: 772–8.
78. Yang SY, Xu GM. Expression of PDGF and its receptor as well as their relationship to proliferating activity and apoptosis of meningiomas in human meningiomas. *J Clin Neurosci* 2001; 8: 49–53.
79. Nagashima G, Asai J, Suzuki R, et al. Different distribution of c-myc and MIB-1 positive cells in malignant meningiomas with reference to TGFs, PDGF, and PgR expression. *Brain Tumor Pathol* 2001; 18: 1–5.
80. Maxwell M, Galanopoulos T, Hedley-Whyte ET, et al. Human meningiomas co-express platelet-derived growth factor (PDGF) and PDGF-receptor genes and their protein products. *Int J Cancer* 1990; 46: 16–21.
81. Kirsch M, Wilson JC, Black P. Platelet-derived growth factor in human brain tumors. *J Neurooncol* 1997; 35: 289–301.
82. Johnson MD, Woodard A, Kim P, et al. Evidence for mitogen-associated protein kinase activation and transduction of mitogenic signals by platelet-derived growth factor in human meningioma cells. *J Neurosurg* 2001; 94: 293–300.
83. Todo T, Adams EF, Fahlbusch R, et al. Autocrine growth stimulation of human meningioma cells by platelet-derived growth factor. *J Neurosurg* 1996; 84: 852–8.
84. 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.
85. Mawrin C, Sasse T, Kirches E, et al. Different activation of mitogen-activated protein kinase and Akt signaling is associated with aggressive phenotype of human meningiomas. *Clin Cancer Res* 2005; 11: 4074–82.
86. Johnson MD, Okedli E, Woodard A, et al. Evidence for phosphatidylinositol 3-kinase-Akt-p7S6K pathway activation and transduction of mitogenic signals by platelet-derived growth factor in meningioma cells. *J Neurosurg* 2002; 97: 668–75.
87. 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.
88. Lamszus K. Meningioma pathology, genetics, and biology. *J Neuropathol Exp Neurol* 2004; 63: 275–86.
89. Kerbel RS. Tumor angiogenesis. *N Engl J Med* 2008; 358: 2039–49.
90. Cook KM, Figg WD. Angiogenesis inhibitors: current strategies and future prospects. *CA Cancer J Clin* 2010; 60: 222–43.
91. Lamszus K, Lengler U, Schmidt NO, et al. Vascular endothelial growth factor, hepatocyte growth factor/scatter factor, basic fibroblast growth factor, and placenta growth factor in human meningiomas and their relation to angiogenesis and malignancy. *Neurosurgery* 2000; 46: 938–47.
92. Provias J, Claffey K, delAguila L, et al. Meningiomas: role of vascular endothelial growth factor/vascular permeability factor in angiogenesis and peritumoral edema. *Neurosurgery* 1997; 40: 1016–26.
93. Goldman CK, Bharara S, Palmer CA, et al. Brain edema in meningiomas is associated with increased vascular endothelial growth factor expression. *Neurosurgery* 1997; 40: 1269–77.
94. Puchner MJ, Hans VH, Harati A, et al. Bevacizumab-induced regression of anaplastic meningioma. *Ann Oncol* 2010; 21: 2445–6.
95. Friedman HS, Prados MD, Wen PY, et al. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. *J Clin Oncol* 2009; 27: 4733–40.
96. Andrae N, Kirches E, Hartig R, et al. Sunitinib targets PDGF-receptor and Flt3 and reduces survival and migration of human meningioma cells. *Eur J Cancer* 2012; 48: 1831–41.
97. Kaley TJ, Wen PY, Schiff D, et al. Phase II trial of Sunitinib (SU011248) for recurrent meningioma. Abstract: 15th Annual Meeting of the Society for Neuro-Oncology (SNO), November 2010.
98. Grimm SA, Chamberlain MC, Chandler J. A phase II trial of PTK787/ZK 222584 (PTK787) in recurrent high-grade meningioma. *J Clin Oncol* 2011; 29: 2046.
99. Collins IM, Beddy P, O'Byrne KJ, et al. Radiological response in an incidental meningioma in a patient treated with chemotherapy combined with CP-751, 871, an IGF-1R inhibitor. *Acta Oncol* 2010; 49: 872–4.