Systemic Treatment of Recurrent Meningioma

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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 ineffective. Immuno-therapy 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 epithelial 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 various 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.

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 neurofibromatosis) 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-
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 (CA V [28]), and, more recently, high-dose chemotherapy (carboplatin, etoposide, and thiothepa) followed by ifosfamide and mesna [27], cisplatin and doxorubicin [26], cyclophosphamide, adriamycin, and vincristine (CA V [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.

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

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.
In this setting, several studies have evaluated the efficacy of systemic treatment in recurrent meningioma patients. The most relevant ongoing trials in recurrent meningioma patients are summarized in Table 2. Table 2. Summary of the most relevant ongoing trials in recurrent meningioma patients. Source: clinicaltrials.gov

<table>
<thead>
<tr>
<th>Agent</th>
<th>Study</th>
<th>Mechanism of action</th>
<th>Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxyurea</td>
<td>Phase II</td>
<td>Ribonucleotide reductase inhibitor</td>
<td>UNICANCER</td>
</tr>
<tr>
<td>Hydroxyurea plus verapamil</td>
<td>Phase II</td>
<td>Ribonucleotide reductase inhibitor Calcium channel antagonist</td>
<td>University of Utah</td>
</tr>
<tr>
<td>Interferon-α</td>
<td>Phase II</td>
<td>Antiproliferative and antiangiogenic activity</td>
<td>M.D. Anderson Cancer Center</td>
</tr>
<tr>
<td>Pasireotide (SOM230B/SOM230C)</td>
<td>Phase II</td>
<td>Somatostatin analogue</td>
<td>National Cancer Institute</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>Phase II, I</td>
<td>EGFR inhibitor</td>
<td>Sidney Kimmel Comprehensive Cancer Center</td>
</tr>
<tr>
<td>Gefinitib</td>
<td>Phase II</td>
<td>EGFR inhibitor</td>
<td>Memorial Sloan-Kettering Cancer Center</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>Phase II</td>
<td>VEGF and PDGFR inhibitors</td>
<td>University Magdeburg</td>
</tr>
<tr>
<td>Imatinib mesylate</td>
<td>Phase II</td>
<td>PDGFR inhibitor</td>
<td>Istituto Scientifico H. San RaffaeI</td>
</tr>
<tr>
<td>Imatinib mesylate</td>
<td>Phase II</td>
<td>PDGFR inhibitor</td>
<td>Northwestern University</td>
</tr>
<tr>
<td>Hydroxyurea</td>
<td>Phase II</td>
<td>Ribonucleotide reductase inhibitor</td>
<td>Sarah Cannon Research Institute</td>
</tr>
<tr>
<td>Valatanib</td>
<td>Phase II</td>
<td>VEGF and PDGFR inhibitors</td>
<td>Northwestern University</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>Phase II</td>
<td>VEGF antibody</td>
<td>M.D. Anderson Cancer Center</td>
</tr>
<tr>
<td>Everolimus</td>
<td>Phase II</td>
<td>mTOR inhibitor</td>
<td>National Cancer Institute</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>Phase II</td>
<td>VEGF antibody</td>
<td>Burzynski Research Institute</td>
</tr>
<tr>
<td>Isisinesib</td>
<td>Phase I</td>
<td>Inhibitor of kinesin spindle protein</td>
<td></td>
</tr>
<tr>
<td>Antineoplastona</td>
<td>Phase II</td>
<td>Modulates ras oncogene, gene PS3</td>
<td></td>
</tr>
</tbody>
</table>

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

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 DFS 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% [49]. 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 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 EGFR 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-
Conclusions

Conflict of Interest

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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25. Granberg SM, Rankin C, Twantes J, et al. Phase III double-blind randomized pla- 


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