Reappraisal of the role of endocrine therapy in meningioma management

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Abstract

Recurrent meningiomas constitute an uncommon but significant problem after standard therapy failure. Speculation that meningiomas may be subject to endocrine influence was supported by both immunohistochemical analyses and epidemiological data. Therefore, alternative strategies such as endocrine therapy have been suggested. Although evidence of consistent findings for the role of specific hormonal exposures is mounting, there are numerous discrepancies about the mitogenic effect of hormonal manipulation on meningioma cells. A better understanding of the molecular mechanisms involved in meningioma pathogenesis may not only lead to the identification of novel diagnostic and prognostic markers but may also facilitate the development of new pathogenesis-based targeted strategies. This review of literature aims to summarize the present state of the art of endocrine therapy in the management of meningiomas, in order to establish whether hormonotherapy could be included in the therapeutic strategy for unresectable and/or progressive tumours in previously irradiated meningioma patients.

Introduction

Meningiomas are common tumours of the central nervous system, which originate from the meningeal coverings of the spinal cord and the brain. Although the cell of origin has yet to be proven, meningiomas are probably derived from arachnoidal cap cells (Riemenschneider et al. 2006). They constitute approximately 13–26% of all intracranial tumours (Bondy & Ligon 1996). For most of those lesions, conventional strategy combining both surgery and radiation therapy provides long-term effective and sufficient clinical results (McMullen & Stieber 2004, Whittle et al. 2004). Surgery is considered as the standard first-line treatment in meningiomas. Its primary goal is the complete removal of the meningioma. However, the decision to operate is guided by the clinical history of the patient, symptoms, accessibility of the tumour and estimation of the clinical benefit achievable by surgery (Bindal et al. 2003). However, some meningiomas recur or are resected subtotally because of anatomical problems such as their location at the skull base and are deferred to postoperative or salvage radiotherapy. The indications for radiotherapy are atypical or anaplastic meningiomas, recurrences or inaccessible meningiomas. Postoperative radiation therapy after the first resection of benign meningiomas is still controversial. However, it is currently used in cases of incomplete resection or in cases of tumour progression. This unresolved issue should be examined prospectively in a randomized study that compares a policy of watchful waiting versus adjuvant conformal irradiation (EORTC 26021 trial). In a minority of patients, regrowth of tumour tissue after irradiation is a major clinical problem. Supported by promising results in breast cancer treatment (Santen & Harvey 1999, Jones & Buzdar 2004), systemic approaches based on hormone manipulation were tested in those patients with poor functional prognosis, in order to improve their clinical outcome.

In the present review, the main goal was to establish whether hormonotherapy could be included in the therapeutic strategy for unresectable and/or progressive tumours in previously irradiated meningioma patients.
Literature review

An English-language literature search was conducted to identify all published studies assessing hormonal influences on meningiomas, in order to highlight potential prognostic and therapeutic values of endocrine therapy. Data for this review were identified by searches of Medline and Cancerlit. The search terms ‘meningioma’, ‘hormonotherapy’, ‘breast cancer’ and ‘clinical trial’ were used. References identified from within retrieved articles were also used. There was no limitation on year of publication and no abstract forms were included.

Epidemiological background

The aetiology of primary brain tumours remains a controversial issue and the only somewhat well-established risk factors for meningioma are ionizing radiation (Sadetzki et al. 2002, Pettorini et al. 2008). A significant increased risk of meningioma has also been advocated in some hereditary syndromes where the mismatch repair gene or the deletion of neurofibromatosis type 2 gene (NF2) have been associated with the occurrence of cerebral benign tumours (Louis et al. 2007, Claus et al. 2008). Mutations in the NF2 gene probably account for the formation of more than half of all meningiomas (Simon et al. 2007), which are hallmark features of this autosomal dominant disorder caused by germ-line mutations in the NF2 gene on chromosome 22q12 (Baser et al. 2003).

Although a role of head injury for the induction of meningiomas has been suspected, this question cannot be answered definitely. It was suggested that the local alteration of the blood brain barrier might be involved by a consequent massive influx of cytokines into the extravasal space. Moreover, it was also advocated that several genes would be upregulated after traumatic brain injury, including genes controlling transcription regulation, signal transduction and intercellular adhesion (Michael et al. 2005).

In adults’ meningiomas, epidemiological data have identified a ratio of 2:1 in female gender (Carroll et al. 2000). Although a possible hormonal association between breast cancer and meningiomas has not been clarified, the simultaneous occurrence of meningiomas and breast cancer is an unusual but well-known event and several cases have been reported with or without brain metastasis (Brandis et al. 1993, Markopoulou et al. 1998, Maiuri et al. 2002). According to data from the Swedish Cancer Registry and from the United Stated Surveillance, Epidemiology and End Results Program, (Ahsan et al. 1995, Malmer et al. 2000), the increased risk of developing meningioma was reported to be 1.5–1.7 times after breast cancer, with a mean time interval between the diagnosis of breast cancer and meningioma of 99.5 months.

Breast cancer and meningioma present some similar features that might account for their association: both tumours occur most frequently in female in their fifth to seventh decades of life, may grow during the early post partum period and express progesterone and oestrogen receptors (ER) on their cell membranes (Smith et al. 2005, Britt et al. 2007, Hatibolgu et al. 2008). Both clinical case reports and retrospective data reported that meningioma may grow rapidly during periods of relative hormonal excess, during the luteal phase of the menstrual cycle and in the latter trimesters of pregnancy (Wahab & Al-Azzawi 2003). Furthermore, menopause and oophorectomy have been identified as conferring protection against the risk of developing meningiomas, while excess of adiposity is positively associated with the disease (Kannan et al. 2003). Some authors described growth of meningiomas after oestrogen–progestin therapy (Gazzeri et al. 2007). Custer et al. (2006) investigated the association between oral contraception (OC) or hormonal replacement therapy (HRT) and intracranial meningioma in women, using a population-based, matched case–control study. Exposures for 143 cases and 286 controls matched on age within 5 years were obtained by interview. Risk of meningioma appeared modestly elevated in past OC users and in current users. However, the confidence intervals were wide and no significant association between meningioma risk and duration of OC use was found. Discrepant results were recently obtained by Blitshteyn et al. (2008). Authors retrospectively reviewed a total of 1390 women with a history of symptomatic or incidentally discovered meningiomas, 156 (11%) of whom were either current or past HRT users. A logistic regression analysis, adjusted for age, demonstrated a significantly positive association between a diagnosis of meningioma and HRT use. Similarly, Wigertz et al. (2006) also found an increased relative risk of meningioma among post-menopausal women for ever-use of HRT. Further evaluation of exogenous hormone use in women with meningioma is needed with particular attention to stratification by hormonal receptor status, duration of and age at use as well as tumour receptor subtype (Claus et al. 2007).

Whereas alterations of the BCRA1 and BCRA2 are not common pathogenic events in the development of meningiomas (Kirsch et al. 1997), the correlation between breast cancer and meningioma raises the question of a common pathogenic mechanism. Several
studies have shown that hyperinsulinaemia could promote carcinogenesis in breast cancer. This mechanism might possibly involve activity of insulin growth factor I (Stoll 1999, Hudelist et al. 2007). Kaplan et al. (1997) have noticed an association between meningioma and intake of saturated fat. As gene expression of different insulin-like growth factors has also been reported in meningioma, it is therefore of interest to delineate a possibility of hyperinsulinaemia as a triggering factor in both meningioma and breast cancer. Other authors hypothesized that because obesity affects male steroid hormone synthesis, male patients with meningiomas might exhibit a high obesity rate, suggesting a hormonal influence on meningiomas in men as well as women (Aghi et al. 2007).

Moreover, the human progesterone receptor (PGR) gene shares the same location as the mammary oncogene FGFR3 in chromosomal 11q13 (Law et al. 1987). Although this proximity may explain the role of progesterone in breast cancer, the role of oncogene FGFR3 in the genesis of meningiomas is not yet known. Besides, both meningiomas and breast cancers over-express the MYC oncogene. Claus et al. (2008) measured via immunohistochemistry PGR and ER from 31 meningioma patients undergoing neurosurgical resection and compared with gene expression profiling results. Genes on the long arm of chromosome 22 and near the NF2 gene were most frequently noted to have expression variation, with significant up-regulation in PGR-positive versus PGR-negative lesions, suggesting a higher rate of 22q loss in PGR-negative lesions.

It remains difficult to interpret the results from epidemiological trials that are most often biased and retrospectively analysed. Epidemiological reports frequently include all women regardless of menopausal status. Moreover, effects of exogenous hormones are not the main hypothesis examined. Another weakness of those studies is the lack of detailed information on when in time the patients had taken hormones and what types of compounds they had used. Epidemiological background, including female predominance in meningiomas incidence, suggested that growth of meningiomas is hormone dependent. Growing evidence of a hormonal association between meningiomas and breast cancer incites to focus on the predictive value and therapeutic consequences of hormonal status in alternative strategies for patients with unresectable and/or already irradiated progressive meningioma. However, it is obvious that further studies remain necessary.

**Hormonal receptors status and patients’ outcome**

It has been demonstrated that most of meningiomas express hormone receptors on their cell membranes, although to a variable extent (Marosi et al. 2008). Actually, up to 90% of meningiomas express PGR, while fewer 30 to 48% express ER (Korhonen et al. 2006). Omulecka et al. examined samples from 64 tumours and demonstrated a positive immunoreaction for PGR in 100% meningothelial, 95% transitional, 46% fibrous and 78% atypical variant of meningiomas. Besides, intensity of immunoreaction was stronger in grade I than in grade II tumours (Omulecka et al. 2006). In the past two decades, the relationship between sexual hormone receptors and meningiomas has been the subject of several studies (Markwalder et al. 1988, Perrot-Applanat et al. 1992, Nagashima et al. 1995, Blankenstein et al. 2000, Fewings et al. 2000, Gursan et al. 2002, Strik et al. 2002), providing sufficient evidence that the expression of PGR by meningioma cells is a prognostically favourable sign. In opposite, loss of this expression would be accompanied by a more aggressive tumoral behaviour. Pravdenkova et al. advocated that the expression of the PGR alone in meningiomas signals a favourable clinical and biological outcome. A lack of receptors or the presence of ER correlates with an accumulation of qualitative and quantitative karyotype abnormalities, a higher proportional involvement of chromosomes 14 and 22 in de novo tumours and an increasing potential for aggressive clinical behaviour, progression and recurrence of meningiomas (Pravdenkova et al. 2006). These results seem to be consistent with those from a long-term prospective analysis of 62 meningiomas in 53 patients. Although no association could be demonstrated between recurrence and patient’s gender, extent of resection, histological subtype or tumour site, there was a significant association between recurrence and negativity for PGR status ($P=0.013$), indicating that benign meningiomas that are PGR positive are less likely to recur (Fewings et al. 2000). Roser et al. (2004b) also established that a significant correlation between negative PGR expression and high tumour vascularity with high Ki-67 labelling index (LI), which combined with TP53 labelling indices, would be a useful additional tool in discriminating atypical from benign or anaplastic meningiomas, especially in histological borderline cases. Besides, Ki-67 is an important predictive tool of meningioma natural history (Bruna et al. 2007, Terzi et al. 2008). However, recent results from a retrospective analysis of 55 patients with benign meningiomas could not
demonstrate a correlation between PGR expression and patterns of recurrence after seemingly complete removal (Mairui et al. 2008).

Strik et al. reported the role of PGR expression on relapse in the long-term clinical course of 93 benign meningiomas. Authors assessed the expression of PGR and the proliferation marker mindbomb homolog 1 (MIB-1) in the primary tumours of 30 cases of benign, completely resected, recurrent meningiomas, when compared with 63 cases of meningiomas without recurrence for 14 or more years (Strik et al. 2002). They concluded to significantly higher risk for recurrence (odds ratio 3.53) for tumours with a low expression of PGR. These findings support previous studies and demonstrate an association between low expression of PGR and higher risk of recurrence. In a recent retrospective study of 31 patients with meningioma undergoing neurosurgical resection, PGR and ER were measured via immunohistochemistry and then compared with gene expression profiling results. After examination of gene expression for meningioma cases by hormone receptor status, Claus et al. (2008) established a stronger association with PGR than with ER status. Maiuri et al. also concluded from 50 completely resected benign (WHO I) meningiomas that higher mitotic index, Ki-67 LI, and PGR negativity had a strong predictive value of recurrence ($P < 0.0001$), particularly when BCL-2 positivity is associated. In opposite, the ER status was not relevant (Maiuri et al. 2007). Although the role of sexual steroid hormones in genesis of meningiomas is yet not clarified, there is growing evidence that progesterone may at least contribute to the growth of PGR-positive meningiomas (Marosi et al. 2008). This suggests that PGR status may be a clinical marker for genetic subgroups of meningioma and warrant further examination.

Almost all studies frequently included meningiomas with different resection grades, histological subtypes and a substantial number of atypical meningiomas. Sexual hormone receptor status should routinely be studied for its prognostic value especially in female patients and should be taken into account in tumour grading. Besides, the initial receptor status of a tumour may change in the progression or recurrence of tumour, thus have some prognostic and therapeutic implications. Moreover, there has been a long-standing debate in the literature as to whether the PGR that are present in meningiomas are functional. In contrast to breast cancer, the PGR/ER receptors in meningiomas are probably not functional in all tumours (Speirs et al. 1997). Abnormally spliced forms of ER have been reported in human meningiomas, which do not bind the ligand, but may constitutively induce PGR expression. The presence of ER variants might explain the autonomous expression of PGR in meningioma (Koehorst et al. 1993). However, it was suggested that promegestone (R5020), a progesterone agonist, would increase transcription only in meningioma cell cultures that express the PGR, supporting the concept that progestins may play a role in meningioma growth (Carroll et al. 1995). It remains to be elucidated whether these transcripts are or will be translated to a biologically active protein. These considerations may explain why the breast cancer drugs do not affect meningioma growth in a desirable way.

No association between PGR status or proliferation LI and variables such as tumour location, first-time resection versus reoperation, and histological subtype has been reported in the literature so far. However, significantly higher MIB-1 indices have been found in recurrent than primary meningioma (Wolfsberger et al. 2004). As these patients represent the best candidates for adjuvant hormonal therapy, further assessment of these potential changes remains necessary.

**Endocrine therapy**

Epidemiological and immunohistochemical data have led to some attempts of treatment with anti-hormonal therapies for patients with PGR-positive meningioma (Strik et al. 2002). After repeated surgery and radiotherapy, the number of patients affected by recurrent, progressive and symptomatic meningiomas is small. However, these patients with poor prognosis represent a major therapeutic challenge. Few data are available on benefit of hormonotherapy in unresectable meningioma on progression. Supported by promising results in breast cancer treatment, new chemotherapeutic approaches based on hormone manipulation were tested in patients with meningioma, making long-term anti-progestational therapy a logical treatment strategy (Grunberg 1994). Postoperative radiation is currently used in cases of incomplete resection or tumour progression. For that reason, reports that assessed the role of endocrine therapy in meningioma management included patients with progressive disease after either postoperative radiotherapy or primary radiotherapy.

Mifepristone (RU486) is an oral anti-progestational commonly used in adjuvant strategy or metastatic treatment of ER-positive breast cancer with a significant benefit in global survival. Mifepristone inhibits the transcriptional activity of PGR by complex mechanisms at concentration much lower than progestins (Edwards et al. 2000). The use of progesterone antagonists in the palliation of meningioma has been discussed repeatedly for more than 10 years.
found in eight patients, seven of whom were male or premenopausal female, which can result in significant clinical benefit in this subgroup of patients (Grunberg et al. 2006). The only prospective study on this topic was conducted on 160 patients. Eighty patients were treated with mifepristone 200 mg and 80 patients were treated with placebo for a median duration of 10 months. Grade IV toxicities were experienced by six patients in the mifepristone arm, whereas one patient had grade IV toxicity in the placebo arm. Grade III toxicities were seen in 30 patients in the mifepristone arm and in 24 patients in the placebo arm. Most of reported toxicities were fatigue (72 vs 54%), headache (44 vs 41%) and hot flushes (38 vs 26%). Besides, several female patients developed endometrial hyperplasia. This trial was prematurely closed and is yet to be published. Neither trend nor difference was observed between the two arms in terms of time to progression: 55% of patients had stable disease, 1% of patients had partial response and no patient could achieve complete response (Newfield et al. 2001).

Tamoxifen is an orally active selective ER modulator that competitively binds to ER, producing a nuclear complex that decreases DNA synthesis and inhibits oestrogen effects. Markwalder et al. (1985) reported six patients with meningiomas treated with tamoxifen and found no significant change in tumour growth with drug treatment. In this small study, survival at 72 months was 72%, whereas it has been reported to be 71% with subtotal resection alone. In a phase II evaluation of an hormonotherapy by tamoxifen given 40 mg/m² b.i.d. for 4 days, then 10 mg b.i.d. thereafter in unresectable or refractory meningiomas, Goodwin et al. observed only one patient (5%) achieving a partial response while two had a minor response measured on computed TDM that was of short duration (4 and 20 months). Six patients (32%) remained stable for a median duration of more than 31 months while 10 (53%) demonstrated progression. Whereas 22% reported subjective improvement, this did not correlate with objective improvement in all cases, and a definite recommendation for the use of tamoxifen in refractory meningiomas could not be made (Goodwin et al. 1993). Published data on meningiomas endocrine therapy in preclinical and clinical settings are reported in Table 1.

From clinical results to molecular pathways
Steroid hormone receptors belong to a large superfamily of nuclear receptors that bind DNA at specific sites to control gene transcription (Savouret et al. 2008).
Table 1 Effects of endocrine therapy on growth of meningiomas

<table>
<thead>
<tr>
<th>Material</th>
<th>Endocrine agent</th>
<th>TD (m)</th>
<th>Results</th>
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<tr>
<td>Olson et al. (1986)</td>
<td>In vitro</td>
<td>Three tumours (A, B and C) in experimental media</td>
<td>TAM</td>
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<td></td>
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<td>RU486</td>
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<td>Markwalder et al. (1985)</td>
<td>6</td>
<td>Inoperable/recurrent tumours</td>
<td>TAM</td>
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<td></td>
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<td>17 β-E2 + PG</td>
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<tr>
<td>Lamberts et al. (1992)</td>
<td>12</td>
<td>Inoperable/recurrent with evidence of recent tumour growth</td>
<td>RU486</td>
</tr>
<tr>
<td>Goodwin et al. (1993)</td>
<td>19</td>
<td>Inoperable refractory meningiomas</td>
<td>200 mg/m²</td>
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<td></td>
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<td>TAM</td>
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<tr>
<td>Newfield et al. (2001)</td>
<td>160</td>
<td>Randomized trial of unresectable/progressive meningiomas</td>
<td>RU486 versus placebo</td>
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<tr>
<td>Grunberg et al. (2006)</td>
<td>28</td>
<td>Inoperable meningiomas</td>
<td>RU486</td>
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TD, treatment duration; P, prospective; NA, not applicable; m, months; TAM, tamoxifen, PG, progesterone; 17 β-E2, 17 β-oestradiol; UP, until progression; RU486, mifepristone; PFS, progression free survival.
However, the mechanisms by which steroid receptors modulate the transcription of target genes remain under investigation. The existence of interactions between steroid hormones and peptide growth factors has also been reported (Murphy et al. 1986). After interaction with ligand, the receptors undergo conformational changes. Consequently, dimers of receptors recognize specific regulatory DNA sequences upstream of several target genes. Activated receptors direct the assembly and the stabilization of a preinitiation complex that might conduct transcription of these genes (Carroll et al. 2000). Several coactivators that are associated in a ligand-dependent manner have been identified, enhancing transactivation of target genes (Horwitz et al. 1996). It was demonstrated that the expression of the steroid coactivators steroid receptor cofactor (NCOA1), amplified breast cancer protein (NCOA3) and transcriptional intermediary factor 2 (NCOA2) in most of meningiomas (Carroll et al. 2000). Better characterization of coregulators would be necessary and may partially explain the wide heterogeneity in response to endocrine therapy. The complex process of transcriptional activation of the steroid hormone receptors may be influenced by the relative amount of these components. Modulation in expression of patterns of the concerned genes suggests that their expression may be tissue dependent. If hormonal therapy has a direct action on the PGR, these patients should respond best to anti-progesterone treatment. A major obstacle in understanding the molecular changes that lead to meningioma formation and progression is the lack of appropriate in vitro and in vivo model systems. It was suggested that the relative expression of coactivators in meningiomas may contribute to heterogeneity of hormonal responses and to discrepancies about the mitogenic effect of steroids on meningiomas in both in vitro and in vivo models.

Another explanation would be that the postulated anti-proliferative effect of hormonal modulation may appear only in patients with highly differentiated tumours, probably not in patients with multiple recurrences or with atypical or anaplastic meningioma on progression after aggressive conventional therapies. PGR-positive cells in all histological grades are distributed heterogeneously throughout the tumour and it is still unclear whether areas of PGR positivity in meningiomas reflect the status of the whole tumour (Brandis et al. 1993). Because of modern microsurgical techniques, where only tumour parts are deferred to the pathologist, there is a subsequent risk of over- or underestimation of focal accumulation of biological activity within the meningioma. As PGR index is variable in meningioma, depending on clinical parameters and histopathological features, stratification on the basis of PGR index should be considered for further anti-progesterone therapy trials (Wolfsberger et al. 2004).

At least two PGR isoforms have been found, PGR-B and PGR-A, each of which are likely to have different biological functions. While both isoforms have similar DNA and ligand-binding affinities (Lessey et al. 1983, Graham et al. 1996), they exhibit different regulating properties. PGR-A is considered to be a dominant negative transrepressor whereas PGR-B is a strong transactivator (Wen et al. 1994). It was demonstrated that meningiomas contain both isoforms in variable ratios, but most of meningiomas express more PGR-A than PGR-B. This variability may have some biological significance. It was assumed that progesterone responsiveness could be based on transrepression rather than on transactivation of target genes. Progesterone blockade may only be effective in certain subsets of meningiomas (Verheijen et al. 2001).

Rubinstein et al. compared hormone receptors in initially excised versus recurrent intracranial meningiomas. Although minor changes in the PGR status induced by radiotherapy should not be excluded, authors demonstrated that these receptors persisted in recurrent meningiomas and even significantly increased ($P<0.02$; Rubinstein et al. 1994). In MCF7 breast cancer cell lines, Paulsen et al. (1996) demonstrated that a radiation dose of 6 Gy reduced the ER content in cytosol, but brought no alterations to the PGR content. These results support hormone treatment for non-resectable meningiomas, especially at recurrence. However, it should not be excluded that functional changes in molecular mechanisms may affect a possible hormonotherapy. This should be further assessed, in order to better understand the reason for such discrepancies in clinical trials, most of them including patients previously irradiated.

**Conclusion**

The place of hormonotherapy in meningioma remains unclear. Results from the present analysis of literature are that the PGR status combined with the routine pathological investigation can provide more insight into the behaviour of meningioma, particularly in histopathological borderline cases (Roser et al. 2004a). However, the PGR status alone cannot be used to predict behaviour in benign meningiomas and should not influence the decision about follow-up intervals and therapeutic strategies. In the specific case of unresectable meningioma residue in progression after ionizing radiation, clinical chronology and data of literature
incite to propose inclusion into a therapeutic trial. Understanding of pathways of steroid-mediated transactivation should allow new approaches in the treatment of meningiomas in order to improve the patients’ outcome (Whittle et al. 2004). Together with routine histological evaluation, hormonal status should help to describe the biological behaviour of meningiomas. Combination of both clinical and biological features will help to devise more effective follow-up strategies.

Although the underlying genetic causes are unknown, meningiomas’ growth is sustained by the dysregulated expression of steroid hormones, growth factors, their receptors and activation of signal transduction cascades. Multiple new targeted agents, such as anti-angiogenic therapies, will be investigated in early phase trials for patients with recurrent or progressive disease after standard therapy has failed. However, hormonotherapy has probably been early classified as ‘out of date’. Wide heterogeneity in terms of clinical outcome and response to targeted treatment exists. Thus, further works should be focused on the identification of better biologic and clinical factors that may serve as prognostic and predictive markers. Moreover, future advances in basic research and genomics should improve our understanding of the biologic basis of the meningioma development and progression (Lusis et al. 2005, Loussouarn et al. 2006). Use of array-based approaches of global genomic and gene expression analyses and new in vitro and in vivo models may contribute to further development of new targeted therapies, particularly for patients for whom surgical and radiation options have been exhausted.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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