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Antiangiogenic Treatment of Meningiomas

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Opinion statement

Meningiomas are the most common intracranial tumors and the majority of cases is curable by surgical resection. Incompletely resected tumors and tumors with signs of increased malignancy (WHO grade II and III tumors) are prone to recur. In meningiomas relapsing after surgical resection and after exhaustion of radiotherapeutic options, drug therapy is to be considered. A variety of drugs has been studied in meningiomas, including hydroxyurea, temozolomide, irinotecan, interferon-alpha, mifepristone, octreotide analogues, megestrol acetate, bevacizumab, sunitinib, vatalinib, imatinib, erlotinib, and gefitinib. Unfortunately, most of these agents have shown no or very limited activity against meningiomas and cannot be recommended for clinical use. Compounds with antiangiogenic properties, i.e., bevacizumab, sunitinib, and vatalinib have shown potential efficacy in uncontrolled studies and should be investigated further, ideally in randomized clinical trials. Emerging clinical studies will evaluate novel medical treatment approaches including the tetra-hydroisoquinoline alkaloid trabectedin (European Organisation for Research and Treatment of Cancer (EORTC) phase II trial 1320) and SMO or AKT inhibitors in molecularly selected cases.

Introduction

Meningiomas are the most frequent intracranial tumors [1, 2]. Most meningiomas are benign, are considered as grade I tumors by the WHO, and are curable by surgical resection. However, tumors that are not completely resectable, e.g., due to their localisation in inaccessible locations such as the skull base, and tumors with histological signs of increased malignancy (WHO grade II and III meningiomas) tend to progress/recur after surgical resection. Salvage treatment for such cases usually comprises re-resection or radiotherapy and, if neither of these options is feasible, systemic drug therapy. A variety of drugs has been studied in meningiomas, including hydroxyurea, temozolomide, irinotecan, interferon-alpha, mifepristone, octreotide analogues, megestrol acetate, bevacizumab, sunitinib, vatalinib, imatinib,

erlotinib, and gefitinib. Unfortunately, most of these agents have shown no or very limited activity against meningiomas and cannot be recommended for clinical use. Based on a recent comprehensive literature review, only bevacizumab, sunitinib, and vatalinib have shown potential clinically relevant activity in the available studies (Table 1) and will be discussed in more detail in this article [3••]. Indeed, antiangiogenic agents seem to provide rational treatment opportunities against meningioma, as upregulation of angiogenic pathways has repeatedly been described in these tumors [4–6]. Emerging clinical trials will evaluate novel medical treatment approaches based on preclinical data [7]. The European Organisation for Research and Treatment of Cancer (EORTC) phase II trial 1320 will compare in a randomized fashion the tetra-hydroisoquinoline alkaloid trabectedin with local standard of care in recurrent grade II and III meningiomas [8]. Furthermore, a clinical trial evaluating specific inhibitors in meningiomas bearing *SMO* or *AKT* mutations is being launched [9, 10••, 11••].

Pharmacologic treatment

Vatalanib (PTK787/ZK 222584)

Vatalanib is an oral inhibitor of VEGFR1 (Flt-1), VEGFR2 (KDR), and VEGFR3 (Flt-4) and has antiangiogenic properties. Vatalanib was evaluated in a single-arm phase II trial in recurrent or progressive radiation and surgery refractory meningiomas (Table 1) [12••]. This study enrolled 25 patients (2 WHO grade I meningiomas, 14 WHO grade II meningiomas, 8 WHO grade III meningiomas, 1 hemangiopericytoma). Grade II patients had a progression-free survival (PFS)-6 of 64.3 %, a median PFS of 6.5 months, and an overall survival (OS) of 26.0 months. Grade III patients had a PFS-6 of 37.5 %, median PFS of 3.6 months, and OS of 23 months. These efficacy results appear promising in relation to historical control data [3••].

Standard dosage	Vatalanib was orally administered to meningioma patients at a continuous dose of 500 mg twice daily.
Contraindications	The toxicity profile of vatalanib and the clinical patient history needs to be considered before prescribing this drug.
Main drug interactions	Concurrent administration of enzyme-inducing anti-epileptic drugs and P450 enzyme inhibitors such as grapefruits should be prevented.
Main side effects	The most common adverse events seen in meningioma patients included fatigue (60 %), hypertension (24 %), and elevated transaminases (24 %) [12••].
Special points	The available and promising single-arm phase II data in meningioma should be validated in a randomized clinical trial.

Table 1. Results of studies on antiangiogenic agents in meningioma

Drug	*n* patients	PFS-6 (%)	Citation
Vatalanib	21	37.5	Raizer et al.
Sunitinib	36	42	Kaley et al.
Bevacizumab	14	85.7	Lou et al.
Bevacizumab	15	43.8	Nayak et al.
Bevacizumab	15	93	Nunes et al.

Sunitinib (SU011248)

Sunitinib is an orally administered small tyrosine kinase inhibitor targeting vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), and KIT. A recent prospective single-arm phase II trial enrolled 36 patients with recurrent and progressive WHO grade II ($n=30$) and III ($n=6$) meningiomas and in addition an exploratory cohort of 13 WHO grade I meningiomas, hemangiopericytoma, and hemangioblastomas (Table 1) [13••]. The PFS-6 rate in the cohort of atypical and anaplastic meningiomas was 42 % and thus reached the predefined efficacy threshold of 30 %. Expression of VEGFR2 in the tumor tissue correlated with favorable PFS.

Standard dosage

Sutinib is approved by the FDA and EMA for metastatic renal cell carcinoma and gastrointestinal stromal tumor (GIST) at a dose of 50 mg daily for 4 of every 6 weeks and for pancreatic neruoendokrine tumors at a continuous daily dose of 37.5 mg. In the phase II trial enrolling patients with meningeal tumors, sunitibin was administered at 50 mg daily for 4 of every 6 weeks [13••].

Contraindications

Neither the FDA nor the EMA prescribing information lists specific contraindications for sunitinib. However, the safety profile of sunitinib and the clinical patient history needs to be considered before prescribing sunitinib. For meningioma patients, the relatively high frequency of intracranial hemorrhages observed needs to be taken into account.

Main drug interactions

Sunitinib should not be given concomitantly with inducers (e.g., rifampicin, phenytoin, carbamazepin, phenobarbiturate) or inhibitors (e.g., ketoconazol, itraconazol, erythromycin, clarithromycin, grapefruit,) of CYP3A4.

Main side effects

The most common side effects of sunitinib are fatigue, diarrhea, nausea, anorexia, hypertension, hand-foot skin syndrome, skin discoloration, and stomatitis. The most severe toxicities include cardial insufficiency, kidney dysfunction, pulmonary embolism, gastrointestincal perforation, and hemorrhages. Among 50 patients with meningial tumors, 30 patients

(60 %) experienced grade 3 or higher toxicities and grade 1 or 2 toxicities were very common [13••]. One patient suffered a grade 5, 1 patient a grade 4, and 2 patients a grade 3 intracranial hemorrhage. In 16 (32 %) patients, a dose reduction and, in 11 (22 %) patients, a discontinuation of sunitinib treatment were required. Dose interruptions and/or dose adjustments of 12.5 mg are recommended based on individual safety and tolerability.

Special points

The available and promising single-arm phase II data in meningioma should be validated in a randomized clinical trial.

Bevacizumab

Bevacizumab is a humanized monoclonal antibody inhibiting VEGF-A and is approved for several cancer types including colorectal cancer, non-small cell lung cancer, kidney cancer, ovarian cancer, breast cancer and, in some countries, glioblastoma. Some retrospective studies and case reports indicate some relevant therapeutic activity against meningioma (Table 1), and two prospective studies evaluating bevacizumab in this setting are ongoing (NCT00972335, NCT01125046) [14••, 15••, 16, 17].

Standard dosage

Bevacizumab is given a s intravenous infusion and approved dosing regimens include 5 or 10 mg/kg of body weight given once every 2 weeks or 7.5 or 15 mg/kg of body weight given once every 3 weeks. Note, however, that bevacizumab is not approved for meningioma and should be administered for this tumor type only within clinical studies.

Contraindications

The prescription recommendations of the EMA list the following contraindications for bevacizumab: hypersensitivity to the active substance or to any of the excipients, hypersensitivity to Chinese hamster ovary cell products, or humanized antibodies and pregnancy.

Main drug interactions

No clinically relevant drug interactions are listed in the prescription information oft he FDA or the EMA.

Main side effects

The most common adverse reactions of bevacizumab (incidence >10 % and at least twice the control arm rate across clinical trials) are epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, rectal hemorrhage, lacrimation disorder, back pain, and exfoliative dermatitis. The most serious adverse events that may necessitate bevacizumab discontinuation include organ perforation or fistula, arterial and venous thromboembolic events, hypertension, posterior reversible encephalopathy syndrome (PRES), proteinuria, and infusion reactions.

Special points

Bevacizumab has marked activity against brain edema and can lead to quick alleviation of tumor-associated brain edema with symptom relief

and decreased corticosteroid need. This effect has been observed in several brain tumor types including gliomas, brain metastases, and also meningiomas [18].

Compliance with Ethics Guidelines

Conflict of Interest

Matthias Preusser declares the receipt of honoraria, research support (unrestricted grants), and travel support (scientific meetings) from Roche, GlaxoSmithKline, Böhringer-Ingelheim, and Bristol-Myers Squibb.
Christine Marosi declares no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by the authors.

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