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Light at the end of the tunnel: towards an effective drug therapy for surgery- and radiation-refractory meningioma

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See the article by Kaley et al, on pages 116–121.

The vast majority of patients with meningiomas are effectively treated by neurosurgery, radiosurgery and/or radiation therapy. However, there are a small number of patients whose meningiomas recur despite repeated therapies.

In this issue, Drs. Kaley, Wen, and colleagues from four American institutions report the results of a single-arm, multicenter phase II trial with sunitinib in patients with surgery and radiation-refractory atypical (grade II) and anaplastic (grade III) meningiomas (n = 36) as well as an exploratory cohort of 13 patients with recurrent benign (WHO grade I) meningiomas, hemangiopericytomas and hemangioblastomas.[1] It is a great and rare moment to participate in the discovery of an effective treatment for patients with previously unmet medical needs. This study describes for the first time that patients with atypical and anaplastic meningiomas without further therapeutic options benefited from therapy with the tyrosine-kinase inhibitor sunitinib. For the first time, a positive result for a prospective study in this setting is reported, fulfilling and even exceeding the predefined efficacy endpoint with an observed rate of 42% of patients remaining progression-free at six months (PFS-6), compared with the predefined efficacy PFS-6 threshold of 30%.

Of note, this was a multicenter investigator-initiated study, emphasizing the rarity of aggressive meningiomas recurring after surgery and radiation. There are indeed only a small number of patients with aggressive meningiomas, meaning that there is low potential for significant sales volumes and thus less interest for drug development by the pharmaceutical industry. Moreover, these patients are frequently symptomatic with headaches, seizures, and a variety of neurological deficits,[2] often requiring complex medication regimens for the treatment of pain and the prevention of seizures that could potentially lead to drug interactions. Most patients also have impaired performance status, making their participation in a study even more challenging.

Recently, the Response Assessment in Neuro-Oncology (RANO) working group reviewed the published evidence of medical therapies in patients with surgery- and radiotherapy-refractory meningioma.[3] They summarized the experience from 47 publications, including retrospective analyses, pilot and phase II trials, and one phase III trial. Fourteen trials with cytotoxic agents involving a total of 265 patients (most of them with recurrent meningiomas WHO grade I) were reported from 1991 to 2012, eleven of them with hydroxyurea and one each with temozolomide, irinotecan, and with a combination of adriamycin, cyclophosphamide, and vincristine. Six publications reported data on treatment with the somatostatin analogue octreotide, with a median progression-free survival ranging from 5 to 15 months, mainly in patients with WHO grade I meningiomas. Further studies with interferon alpha, hormones, bevacizumab, imatinib, erlotinib, or gefitinib confirmed the poor outcome for patients with aggressive meningiomas and failed to demonstrate any efficacy. The main result of this survey was that it allowed the calculation of a weighted average PFS-6 of 29% for WHO grade I meningiomas and 26% for atypical and anaplastic meningiomas. This survey also showed the commitment of patients participating in all those exploratory trials as well as that of their treating physicians in designing and conducting these studies in order to ameliorate the situation of the affected patients. Searching for druggable targets in aggressive meningiomas,[4] Kaley et al. chose sunitinib, an oral tyrosine-kinase inhibitor targeting two pathways involved in meningioma proliferation in vitro, the platelet-derived growth factor receptor (PDGFR) and the vascular endothelial growth factor receptor 2 (VEGFR2), which was found to be upregulated in all meningiomas and whose expression was shown to increase with recurrence.[5] Previous retrospective surveys and phase II trials using imatinib to target PDGFR alpha were limited to a small number of patients and failed to demonstrate any efficacy.[6–7]

In the study reported in this issue, sunitinib was used in the same dosage as for renal cell cancer and this study met its pre-specified endpoint. However, significant toxicity was observed, including one fatal and three additional intracranial hemorrhages, and eleven patients (11/36, 30%) had interruption of therapy because of toxicity. The suggestion of benefit and increased toxicity of sunitinib in meningioma patients contrasts with the relatively good tolerability but lack of efficacy with this agent in patients with recurrent glioblastoma.[8] The favorable PFS results with sunitinib are similar to a small

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retrospective study of bevacizumab in 15 patients with aggressive meningiomas.[9]

Most interestingly, a correlative imaging study showed a reduction of the intratumoral blood flow in nearly all the patients who were examined. It will be of great interest to correlate these data with the observed therapeutic responses and with the target expression of the respective meningiomas. This study represents a real advance in the management of patients with aggressive meningiomas and will guide further research for these sorely afflicted patients.

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