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Multimodality Therapy of Patients with Refractory Meningiomas

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Opinion statement

Recurrent and refractory meningiomas are a clinical challenge and treatment at the time of recurrence is not well delineated. Treatment with surgery and/or radiation remain the mainstay, but each has their limitations and risks. The search for an adjuvant systemic therapy continues and as many of the initially promising approaches have not had reproducible responses. Bevacizumab has shown some efficacy in controlling recurrent disease and could be useful in disease that is multifocal or in close proximity to critical structures. Other targeted therapies, as well as immunotherapy, are being studied and trials are in development. Though we are hopeful that these novel therapies will benefit patients with refractory meningiomas, we approach them with some trepidation. This is due to prior failures of immunotherapy and targeted therapy in central nervous system disease. In addition, there is known difficulty in developing trials and assessing response with these slow-growing tumors.

Introduction

Meningiomas are the most common type of primary central nervous system (CNS) tumors, making up about a third of these cases [1]. They range from benign tumors (WHO grade I), which are slow growing or cured with resection, to malignant tumors (WHO grade III) which have recurrence rates of up to 80% at 5 years [2•]. The assigned WHO grades for these tumors are based on pathologic criteria and are used to estimate the recurrence risk. The vast majority of meningiomas are grade I. About 20% are grade II, or "atypical," and 1–3% are grade III, or "anaplastic" [3••].

The initial standard of care for any symptomatic or progressing meningioma is maximal surgical resection. Extent of resection, based on Simpson criteria, is a well-studied independent factor of progression-free survival (PFS) and overall survival (OS) [4]. Often, a gross total resection (GTR) is curative for lower grade tumors, as recurrence rate in a lifetime for a grade I meningioma is about 30%, after resection [2•]. For anaplastic meningiomas, the resection is followed with radiation therapy (RT), based on studies showing significantly improved PFS at 5 years [5]. For atypical meningiomas, the initial management is not clearly delineated after maximal possible resection. Completely resected atypical lesions are often observed and subtotally resected (STR) lesions are often followed with 54–60 centigray (cGy) of RT, knowing the higher rate of recurrence of incompletely resected tumors [6]. Though, even this approach is debated [7].

Meningiomas in unresectable areas are treated with RT upfront. Traditionally, fractionated external beam radiation (FEBRT) has been used, but the usage of stereotactic radiosurgery (SRS) has increased, both in the newly diagnosed and residual disease setting [8–10]. In most cases, there is no role for systemic therapy in initial treatment.

Resection, with or without RT, is effective in controlling most meningiomas. However, in the setting of recurrent disease, there are less established standards of care [11]. For all meningioma types, 15-year recurrence rates are 24–60% despite GTR and have been reported over 70% after STR [11]. Known risk factors of recurrence include higher grade meningioma, brain or bone involvement, and elevated proliferation index [12]. Repeat surgery, repeat RT, and systemic therapy are most typically used, but based on limited evidence and established guidelines.

Multimodality management of recurrent or refractory meningiomas

Surgery

Surgery, along with RT, is the mainstay of recurrent meningioma treatment. Re-resection is typically reserved for recurrent disease that is becoming symptomatic or is rapidly progressing. Of course, the area of recurrence must be amenable to resection without significant morbidity [13, 14]. The ability to resect a recurrent tumor and the extent of resection are largely based on the expertise of the neurosurgeon. Another consideration may be patient preference for surgery, to avoid any possible radiation toxicity. Endovascular embolization of tumors is another surgical option, but is only recommended in select cases [13].

Despite plentiful data on the morbidity and mortality associated with initial meningioma resection [15], the data on re-resection in these recurrences are sparse. Magil et al. performed an institutional retrospective review of skull-based and non-skull-based recurrent meningiomas. For the latter, 67 cases were reviewed. It was found that 48% of the cases had at least one complication in their postoperative care. Tumors in the middle third of the sagittal plane or presentation with cognitive changes were significantly associated with complication occurrence on multivariate analysis [16]. Prior radiation therapy was not a predictive factor of complication at repeat resection [16]. This high rate of complication could be due to the nature of re-resection, as a large portion of reported complications were impaired wound healing or pseudomeningocele development. Interestingly, the complication rate of non-skull-based re-resections was higher than that of skull-based re-resections [17]. This could be explained by the higher percentage of grade I meningiomas noted in the skull-based cohort, or due to a patient selection bias.

A notable finding of this retrospective review was that the meningioma grade increased upon repeat resection in 22% of the cases. This would have been missed if the recurrence was treated with alternate therapies, such as RT alone. A theoretical benefit of re-resection at progression would be the identification of mutations amenable to targeted therapy. While repeat resection will remain a mainstay of meningioma recurrence, the higher-than-expected-reported complication rate of reoperation should be considered in the management plan and discussions with patients.

Radiation therapy

Radiation therapy also remains a standard component of initial and recurrent meningioma management. However, re-irradiation presents a challenge to the radiation oncologist and a decision must be made with regard to the total radiation dose given to a particular region. SRS is becoming more ubiquitously used in lesions less than 3 cm in maximal diameter [18] and is able to better spare the surrounding brain parenchyma of potential radiation toxicity.

Lin et al. studied 43 patients in whom recurrent meningioma were re-irradiated over a 15-year span using either SRS or FEBRT. The benefit was clear as PFS was 84% higher than reported PFS from medical therapy trials with similar cohorts [19]. Grade I meningiomas had a subsequent 8% recurrence rate, compared with the reported 40% recurrence of a medically treated recurrent grade I meningioma. Over the 26-month time frame, the patients were followed up; there was an incidence of symptomatic radiation necrosis of 15%, which is comparable with previously reported toxicity from FEBRT in skull-based meningiomas of 0–24% [20]. The optimal choice of RT was SRS, but there was no improved PFS associated with SRS over FEBRT.

Wojcieszynski et al. reported similar efficacy with a PFS of 57 months in re-irradiated grade I meningiomas and 8 months PFS for grades II and III recurrences [21]. Kim et al. looked specifically at re-irradiation with SRS and found 33 patients to have a PFS of 60 months for grade I recurrences and 12 months for grades II and III [22].

Though the follow-up intervals of these patients were relatively short, it appears that re-irradiation with FEBRT or SRS is an effective and well tolerated treatment option. When the recurrence is small enough, SRS limits the radiation toxicity to the surrounding brain parenchyma.

Systemic therapies

Thus far, systemic therapies for meningiomas have not provided enough reproducible data to warrant routine use. Prior reviews of systemic therapy in recurrent and non-recurrent settings have argued against the efficacy of almost all other therapies [3••, 23••]. Here, we review that data and discuss novel and upcoming approaches.

Hormonal therapy

Much anticipation was generated when it was discovered that meningiomas expressed hormone receptors. About 2/3 of all meningioma grades harbored receptors for progesterone and androgen [3••]. Early studies did show some possible benefit of hormone receptor antagonists. Koide et al. used mifepristone, a potent antagonist of progesterone, at 200 or 400 mg/day and reported

objective improvement in 25% of meningiomas treated [24]. Grunberg et al. used similar doses of mifepristone and had five out of 14 patients show objective response in tumor size [25]. However, larger subsequent studies have not been able to reproduce this efficacy. A double-blind multicenter phase III trial using mifepristone showed no impact in patients with unresectable meningiomas [26]. It is postulated that the lack of activity may be due to the loss of expression of the progesterone receptor in advanced disease [3••].

Estrogen receptors had been similarly targeted with promising early results. A pilot study did show an initial responder to tamoxifen [27], but follow-up phase II trial showed no definitive benefit, with a minor response in three out of 19 patients [28]. Similarly, expert opinion on androgen receptor antagonists is that they have no useful activity [3••], though no formal studies have been done.

Chemotherapy

The best studied chemotherapeutic in this setting is hydroxyurea, a drug which is often used in proliferative disorders and other cancer types by inhibiting the enzyme ribonucleoside diphosphate reductase in the S phase of replication [29]. Preclinical experimental data demonstrated inhibition of growth of cultured human meningioma cells by inducing apoptosis [30]. Early clinical studies also showed some promise. In a case series, Schrell et al. reported a reduction in tumor size in three out of four patients [30]. This led to publication of several small retrospective studies showing either stable disease or modest response in patients with recurrent or unresectable disease [31–33]. Follow-up phase II clinical trials were unable to replicate these responses [34], and a retrospective review was unable to confirm the prior efficacy in 29 patients [35].

Other chemotherapeutics have been studied. Chamberlain et al. treated 14 patients with malignant meningiomas after surgery and RT with cyclophosphamide, Adriamycin, and vincristine (CAV) regimen. This regimen is traditionally known for treatment of small cell lung cancer. It is unclear how it was originally connected to meningioma treatment, but its possible efficacy was based on a case collection from Wilson et al. at the UCSF from 1968 to 1994, where eight out of 10 patients with malignant meningiomas treated with CAV had no reported recurrence at 5 years [36]. The Chamberlain study found three patients had partial response and 11 had stable disease [37]. The median OS was 5.3 years. Temozolomide was also studied in a phase II trial with 16 patients but no patient demonstrated a neuroradiographic response [38].

Interferon alpha (INF-alpha) had shown promise in preclinical data, suggesting growth inhibition of 70–100% of meningioma cells exposed to mitotic stimuli [39]. This was followed by two studies showing promising responses, with Kaba et al. showing response in five out of six patients and Muhr et al. showing response in nine out of 12 [40, 41]. A prospective phase II study with recurrent grade I meningiomas showed modest efficacy to INF-alpha at 12-week follow-up, but the median survival was just 8 months in these patients [42].

Somatostatin analogues

Somatostatin receptors are expressed in approximately 90% of meningiomas [3••, 43]. An initial study treated 16 patients with the

somatostatin agonist, sandostatin, using a long-acting-release formulation. Each of these patients had been confirmed to have somatostatin receptor expression using a radio-labeled somatostatin agonist with single-photon emission computed tomography (SPECT) scanning. The results were promising as 31% of patients demonstrated a partial radiographic response and 44% achieved PFS at 6 months [44]. However, a subsequent phase II trial with recurrent high grade meningiomas was stopped early due to lack of efficacy [45]. Another somatostatin analogue, pasireotide with higher affinity for somatostatin receptors, was similarly inefficacious. A multicenter phase II trial was conducted showing no radiographic responses and no improvement at 6 month PFS [46].

Targeted agents

Targeted therapy has generated excitement universally as the genomes of many tumors are being studied thoroughly, including meningiomas.

Bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF), has shown modest activity in recurrent meningiomas. This is presumably due to the blockage of angiogenesis in these highly vascular tumors [47]. Nayak et al. showed a 6-month PFS rate of 43.8% with bevacizumab used in atypical or anaplastic meningiomas [48]. This was corroborated by another study showing a 6-month PFS rate of 86%, though it included meningiomas of all grades [49]. A comprehensive review tallied a total of 22 studies encompassing 92 patients and demonstrated a median PFS of 16.8 months with 73% of patients progression free at 6 months [50•]. These findings have made bevacizumab one of the few reputable systemic therapies available to patients with recurrent meningiomas.

The most recent trial data available for bevacizumab in this setting is a phase II prospective study where bevacizumab was used in patients with progressive meningioma of all types. Forty patients were treated and stable disease over 6 months was noted in 100%, 85%, and 82% of grades I, II, and III recurrent meningiomas, respectively [51]. The mean PFS was 22.5 months, 15.3 months, and 3.7 months, for grades I-III, respectively. The results are promising compared with the contemporary meta-analysis listed above by Franke et al. [50•]. The drug was generally well tolerated.

The PI3K/AKT/mTOR pathway has been implicated in the growth of some meningiomas, with AKT1 and PI3KCA mutations identified in 9% and 7% of meningiomas, respectively [52•]. A phase II study targeting the mTOR pathway (everolimus) in meningiomas, along with bevacizumab, showed stable disease in 15 of 17 enrolled patients with 69% of patient's progression free at 6 months [53]. The median OS was 23.8 months. These promising results have encouraged the development of trials targeting the same pathway. Two of these upcoming studies will be discussed in the next section.

Sunitinib, a small molecule tyrosine kinase inhibitor, also targeting VEGF receptors, has shown some efficacy in higher grade meningiomas. Kaley et al. studied sunitinib in WHO grades II and III lesions and reported a 6-month PFS rate of 42% and a median OS of 24.6 months

[54]. However, toxicities were prevalent in the study with patients suffering from hemorrhage, thrombotic microangiopathy, and one gastrointestinal perforation. Imatinib, an inhibitor of platelet-derived growth factor receptors (PDGFR), has also been studied in recurrent meningiomas, but a phase II trial showed no significant responses [55], even in combination with hydroxyurea [56].

Immunotherapy

Du et al. found evidence of increased programmed death-ligand receptor (PD-L1) expression in meningiomas [57]. PD-L1 expression has been correlated with response to immunotherapy such as nivolumab and ipilimumab in other solid organ cancers [58]. This has led to the development of a phase II clinical trial using nivolumab in recurrent meningiomas (NCT02648997) and another phase II using pembrolizumab in refractory atypical and anaplastic meningiomas (NCT03016091.) In other non-CNS cancer types, these agents have been remarkably efficacious and generally well tolerated.

Future direction

As is the case with many other solid tumor neoplasms, including gliomas, the promising next wave of therapy lies in immunotherapy and targeted therapy. Genomic sequencing has revealed that approximately 8% of meningiomas have AKT1 mutations, over 50% have NF2 mutations, and about 5% have SMO mutations of non-NF2 meningiomas [59, 60]. These mutations have already been proven clinically relevant. Non-NF2 meningiomas were nearly always benign and often originating from the skull base. Conversely, NF2 mutant meningiomas tended to be atypical and located in the cerebral or cerebellar hemispheres [60].

These findings have generated much interest in clinical trial development with targeted therapies. A trial targeting AKT1 and SMO mutations is currently underway for progressive meningiomas, NCT02523014. For patients with SMO/PTCH1 mutations, the trial will use vismodegib, the first hedgehog signaling pathway-targeting agent. For patients with NF2 mutations, a focal adhesion kinase (FAK) inhibitor will be used. Another arm of this study is planned for patients with AKT mutations. Other upcoming studies include a phase I trials of the mTOR pathway inhibitor, NCT01880749, and the cyclin-dependent kinase (CDK) inhibitor ribociclib, NCT02933736.

Other trials plan on combining different targeted agents that have shown little efficacy when used alone. Such a trial was developed in France, combining octreotide, targeting somatostatin receptors, with everolimus, targeting the mTOR pathway [61]. The authors had previously shown this combination to be active in meningiomas, in vitro [62]. The preliminary results from this prospective multicentric phase II study are promising, and the combination appears to be active in refractory progressive meningiomas with acceptable toxicity profiles. Of the 20 patients included, four patients demonstrated a decrease in tumor

volume at 3 months. PFS at 6 and 12 months were 58.2% and 38%, respectively.

NovoTTF (Optune) has been used for a number of years in glioblastoma, both in the upfront and recurrent setting. The device is an external cranial device that produces low intensity, intermediate frequency, and alternating electric fields that interfere with cell division and stunt tumor cell growth. NovoTTF showed stable disease in a small pilot study of four out of six patients with recurrent or progressive grade II or III meningiomas [63]. There is an ongoing trial combining the technology with bevacizumab, NCT02847559.

As mentioned previously, there is considerable interest in developing immunotherapy in this setting and trials are underway using checkpoint inhibitor therapy. The finding of Magil et al. that 22% of meningiomas were higher grade at re-resection is significant in that these tumors may also develop a high mutation load upon recurrence [16]. High tumor mutation burden has been correlated with response to checkpoint inhibitor therapy [64]. There is a recently initiated ETCTN phase I/II trial of nivolumab and SRS, with or without ipilimumab, in patients with recurrent grade II or III meningioma, NCT03604978.

Conclusion

Refractory meningiomas remain a clinical challenge and treatment at the time of recurrence remains a topic of debate. Re-resection and RT remain the mainstays of therapy, but each carries their own risk of postoperative morbidity and radiation toxicity, respectively. Little progress has been made in finding adjuvant or maintenance therapy. There remains a dire need for this development, especially in patients with meningiomas which are unresectable, multiple, or in close proximity to radiation-sensitive structures.

Many of the early trials using hormone receptor antagonists, chemotherapy, and specific receptor blockades showed initial promise, but have not had reproducible results. Thus far, bevacizumab is the only agent that has shown efficacy and tolerability in this setting.

A word should be said about the challenges of assessing response in these particularly irregular, slow-growing tumors. This raises a number of challenges in designing clinical trials, including defining outcomes and standardization of response criteria [11, 65, 66]. In a comprehensive review, Kaley et al. recommended progression-free rate at 6 months (PFS-6) to be a benchmark for future studies [66], as it was the only extractable outcome from the 47 studies they had gathered. Additionally, many of the studies compiled, even in this chapter, are of small sample size and increase the likelihood for biases. These factors make reproducibility and meta-analysis of meningioma data onerous.

There is promise in targeted therapies and immunotherapy as knowledge of meningioma genomics further develops and clinical trials are underway. However, the world of neuro-oncology knows better than most that preclinical and translated data from other solid tumors does not often apply to the CNS.

Compliance with Ethical Standards

Conflict of Interest

Haroon Ahmad declares that he has no conflict of interest.
David Schiff previously served as site PI for a trial (funded by Genentech) of bevacizumab in recurrent meningioma. His institution received per-subject payment for trial accrual.

Human and Animal Rights and Informed Consent

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

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