Management of Large Aggressive Nonfunctional Pituitary Tumors

Experimental Medical Options When Surgery and Radiation Fail

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KEYWORDS

• Pituitary adenoma • Macroadenoma • Nonfunctioning pituitary tumor

KEY POINTS

- Pituitary adenomas are generally considered benign tumors; however, a subset of these tumors displays aggressive behavior and carries a poor prognosis.
- Surgical resection is the mainstay of treatment for nonfunctioning pituitary macroadenomas and functioning tumors that do not respond to medical therapy.
- Radiosurgery is effective in treating tumors that are not completely surgically resected.
- There are several medical therapies being developed for aggressive pituitary adenomas; there are no standard therapy regimens, however, and clinical trials are lacking.

INTRODUCTION

Pituitary adenomas are generally considered benign tumors; however, a subset of these tumors displays aggressive behavior and is not easily cured. These tumors may recur quickly after surgery, grow into the cavernous sinus or skull base, or even metastasize throughout, or outside of, the central nervous system (CNS).[1] In these extreme cases, such tumors would be characterized as pituitary carcinomas. Aggressive pituitary tumors usually carry a poor prognosis. Those that metastasize typically carry with them a mean survival time of less than 5 years.[2]

It is generally believed that pituitary carcinomas originate from transformation of previously benign pituitary adenomas.[3] There is probably a continuum along which pituitary adenomas, atypical pituitary adenomas, and pituitary carcinomas exist, with mitotic activity, vascularity, and specific genetic changes all contributing to the biologic behavior of specific tumors.[2] World Health Organization (WHO) criteria for atypical pituitary adenomas include high p53 immunoreactivity, MIB-1 proliferative index greater than 3%, and increased mitoses.[4] One recent series showed a significantly higher percentage of atypical pituitary adenomas being silent corticotropin (ACTH)-type tumors (17%) compared with ACTH-negative nonfunctioning adenomas (2%).[4] This supports the concept that silent corticotroph adenomas are more aggressive than other types of pituitary tumors,[5–7] although not every clinical study supports this.[8]

The protocol for nonsurgical treatment of aggressive pituitary lesions is less standardized than that of other CNS tumors. Several options are available for these difficult cases, including

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multiple transsphenoidal or transcranial surgeries, radiation therapy, and chemotherapy. The purpose of this article is to summarize recent literature on novel treatments for aggressive pituitary adenomas and analyze recent research that points to new therapeutic strategies for these tumors.

NEW SURGICAL TECHNIQUES

Surgical resection is the mainstay of treatment for nonfunctioning pituitary macroadenomas and functioning tumors that do not respond to medical therapy. Currently, a transsphenoidal approach is the method of choice for resection of pituitary adenomas. While microscopic techniques are still in use, the endoscopic technique is gaining ground.[8,9] Complications after endoscopic surgery are generally low, with transient diabetes insipidus being the most common and still under 5% in recent series.[10,11]

Extended transsphenoidal approaches allow access to pituitary adenomas that previously required a transcranial approach, such as dumbbell-shaped tumors and adenomas with large suprasellar extension. However, these extended approaches may increase the rate of complications.[12,13] Extended transsphenoidal approaches have also improved the ability to access the medial and lateral cavernous sinus, and studies have demonstrated the feasibility and efficacy of this approach for some adenomas with cavernous sinus invasion.[14–16]

Three-dimensional endoscopic pituitary surgery is now being used at some centers. This technique has the advantages of endoscopy in addition to the stereopsis that was previously only available with microscopy. Initial impressions of this technology have been positive, with improved depth perception and no increase in operative time or surgical complications.[17,18] Furthermore, the use of 3-dimensional endoscopy does not appear to increase operative risks.[19] A study examining both subjective and objective performance in 2-dimensional versus 3-dimension endoscopy showed surgeon preference for 3-dimensional endoscopes and a measureable benefit of 3-dimensional visualization when practicing simulated surgical tasks.[18,20]

RADIOTHERAPY

Radiation therapy is not recommended for patients with complete tumor resection.[21] However, since presence of residual tumor postoperatively is a predictor of re-enlargement,[22] accurate assessment of the postoperative magnetic resonance image (MRI) is imperative to determine if radiotherapy is required. Stereotactic radiosurgery and fractionated stereotactic radiation have both been shown to be effective in preventing tumor growth after surgery and are typically well tolerated.[23–25] Stereotactic radiosurgery is the most commonly used technique to deliver radiation to pituitary tumors, although several other modalities are available.[26] Complications after radiosurgery for pituitary adenomas include hypopituitarism and less commonly injury to the visual system.[26] Smaller tumor residuals are more responsive to radiotherapy, and hypopituitarism is less common in these situations.[26]

Outcomes from radiosurgery for nonfunctioning pituitary adenomas are generally favorable, with tumor control rates of greater than 90% being reported in some studies and tumor burden reduction occurring in up to two-thirds of patients.[27] Rates of biochemical response to radiosurgery for ACTH-producing tumors range between 42% and 60%, with most patients exhibiting a response in the first 3 years.[28–31] Rates of biochemical response to radiation for growth hormone (GH)-producing adenomas and prolactinomas are probably near 45% and higher with radiation and medical therapy combined.[26] Radiosurgery has also been used for treatment of pituitary carcinomas with less success.[32]

DOPAMINE AGONISTS

Treatment with dopamine agonists is considered the first line of treatment for prolactinomas.[33] Dopamine receptor agonists exert their effects via activation of the D_2 receptor. The most common dopamine agonists used in clinical trials are bromocriptine and cabergoline.[34] Even large or giant prolactinomas may respond to treatment with dopamine agonists, and therefore in most cases surgery should be deferred until after a trial of medical treatment.[35] However, prolactinomas may be resistant to dopamine agonists either primarily or after an initially positive response. In these cases, surgery, radiation therapy or temozolomide may be of use.[36]

Dopamine agonists have been used for treatment of other types of pituitary adenomas as well. GH-producing adenomas may respond to dopamine agonists, either alone or in combination with somatostatin analogs, although at lower rates than prolactinomas.[34] Response to cabergoline is better in acromegaly patients with mildly elevated insulinlike growth factor 1 (IGF-1) levels and in those with prior radiation treatment, while serum prolactin level and immunohistochemistry for prolactin are less important.[37] Nonfunctioning adenomas may express D_2 receptors. and

response to dopamine agonists with reduction in tumor size in some patients has been reported.[38] Corticotroph adenomas may also express D_2 receptors and thus respond to dopamine agonists.[39] Response to dopamine agonists in patients with aggressive pituitary tumors varies from lack of response[40,41] to tumor control or shrinkage, usually with higher doses than the US Food and Drug Administration (FDA)-approved dose for treatment of prolactinomas.[35,42]

SOMATOSTATIN ANALOGS

Somatostatin analogs such as octreotide are used for the treatment of pituitary tumors that produce GH, ACTH, or thyrotropin (TSH). Pasireotide is a new somatostatin agonist with a high affinity for somatostatin receptors that may hold promise for acromegaly, Cushing disease, and silent ACTH clinically nonfunctioning pituitary adenomas.[43] Pasireotide has a high affinity for type 5 somatostatin receptors that are preferentially expressed on corticotroph tumors.[33] A randomized phase 2 trial in patients with acromegaly showed promising results. In this study, patients received octreotide for 28 days followed by 3 different doses of pasireotide in random order, each for 28 days. Twenty seven percent of patients had a biochemical response, and 39% of patients had a 20% or greater reduction in tumor volume after treatment with pasireotide.[44]

Pasireotide has also been used in trials for the treatment of Cushing disease. In a preliminary study with 39 patients, pasireotide was well tolerated, with gastrointestinal symptoms and injection site reactions being the most common adverse effects.[45] Serum cortisol concentrations were reduced in 76% of patients, with 17% of patients having levels that normalized. Given the rigorous inclusion criteria and small sample size of this study, more studies will be needed to determine the efficacy of pasireotide in the treatment of Cushing disease. A phase 3 trial is in progress to assess the efficacy of pasireotide after 7 months of treatment.

TARGETING ANGIOGENESIS

Angiogenesis, the process of new blood vessel growth, is thought to be a key process in tumor growth and has been recognized as a potential therapeutic target for the treatment of neoplasms throughout the body.[46] There are many molecular targets along the angiogenesis pathway, one of the most well studied being vascular endothelial growth factor (VEGF). VEGF is produced by tumor cells and binds to receptors on endothelial cells stimulating blood vessel proliferation and increased tumor vascularity. Pituitary carcinomas have been shown to exhibit a higher density of microvasculature than adenomas.[2] PTTG, a pituitary tumor oncogene, has been shown to drive increased angiogenesis.[47] There is 1 report of the use of bevacizumab, an anti-VEGF antibody, for treatment of pituitary carcinoma.[48] The patient in this study was initially diagnosed with a silent corticotroph adenoma, a particularly aggressive subtype of pituitary adenoma,[6] that recurred after multiple surgeries and eventually metastasized to the spine. The patient underwent multiple surgeries, treatment with temozolomide, and radiotherapy for the pituitary lesion and spinal metastasis. Because the tumor expressed VEGF, the authors initiated treatment with bevacizumab, with stabilization of tumor growth thereafter. In vitro studies have also shown angiogenesis to be a potential target for treatment of aggressive pituitary tumors, with antibodies against VEGF reducing pituitary tumor size in mouse models.[49,50]

Downstream effectors in the VEGF signaling pathway may also be viable targets for chemotherapy targeting pituitary adenomas. mTOR is a protein kinase in the VEGF signaling pathway that leads to the expression of hypoxia-inducible factor, cell survival, and angiogenesis. One study examining the use of everolimus, an mTOR inhibitor, for treatment of a temozolomide-resistant pituitary carcinoma did not show success.[51] Further studies examining inhibitors of VEGF and its downstream signaling pathways will be needed before antiangiogenic therapy becomes a mainstay of medical treatment for pituitary adenomas.

TEMOZOLOMIDE

Temozolomide is a second-generation oral alkylating agent used primarily in the treatment of glioblastoma. It impairs DNA replication and induces apoptosis by methylating DNA at the O^6 position of guanine.[52] It is useful in the treatment of central nervous system tumors, because it readily crosses the blood–brain barrier. Although the optimal dosing and duration of therapy have not been defined, recent reports suggest that temozolomide is effective in pituitary tumors that are resistant to multimodality therapy.[32,48,53]

Tumors with high levels of O-6-methylguanine-DNA methyltransferase (MGMT) expression are resistant to temozolomide-induced cytotoxicity. The MGMT DNA repair enzyme removes alkyl groups from the O^6 position of guanine, preventing temozolomide-induced cytotoxicity. Epigenetic silencing of the MGMT gene by hypermethylation of its promoter results in accumulation of

temozolomide-induced mutations. Low levels of MGMT expression were associated with longer survival in patients with temozolomide-treated glioblastoma.[54] A significant proportion of pituitary tumors exhibit low levels of MGMT expression. Although initial studies suggested that MGMT expression level is inversely correlated with response to temozolomide,[55–59] subsequent studies indicated a poor predictive value of only 53% based on MGMT expression.[58]

Temozolomide has been used for the treatment of pituitary tumors resistant to multimodal therapy. A report from Kovacs and colleagues[60] described a 42 year-old man with a prolactin-producing adenoma refractory to multiple transsphenoidal resections, radiotherapy, and treatment with bromocriptine, pergolide, and cabergoline, who was treated with temozolomide. Morphologic study of the tumor showed evidence of tumor cell injury. Mohammad and colleagues[61] reported marked clinical improvement and radiological evidence of tumor shrinkage in 3 patients with Cushing disease and aggressive macroadenomas treated with temozolomide. Subsequent reports have confirmed the efficacy of temozolomide in aggressive prolactin-producing tumors, corticotroph-producing tumors, GH-producing tumors, gonadotroph-producing tumors, and nonfunctioning adenomas.[53,61]

Temozolomide has also been used successfully in the treatment of patients with pituitary carcinoma. Fadul and colleagues[32] treated a 38-year-old man with a gonadotropin-producing pituitary carcinoma with temozolomide after unsuccessful treatment with octreotide and radiation therapy. The patient's pain and visual field deficits improved, and he was asymptomatic 16 months after completing treatment. More recent reports confirm the efficacy of temozolomide in the treatment of pituitary carcinomas, with patients exhibiting both clinical and radiographic responses.[53,60–65] The authors have used temozolomide in one patient with a pituitary carcinoma; however, the patient exhibited tumor progression and hematological toxicity during the course of her therapy (Ioachimescu and Oyesiku, 2010, personal communication).

Although further research is indicated to clarify the role of temozolomide in treatment of aggressive pituitary tumors, patients who exhibit a progressive course postoperatively should be considered for a trial of temozolomide regardless of MGMT expression.

GLIADEL WAFERS

Gliadel, a bischloroethyl-nitrosourea (BCNU)-impregnated wafer, has been approved by the FDA for treatment of recurrent gliomas. BCNU is a nitrosurea that exerts its effects by alkylating DNA. With the ability to bypass the blood–brain barrier and first pass metabolism by the liver, chemotherapy delivered intraoperatively to brain tumors holds promise as a means to deliver high doses of chemotherapeutics while avoiding systemic adverse effects. In trials for treatment of recurrent gliomas, Gliadel has shown to be effective and well tolerated in patients with gliomas.[66] Only one study has examined the use of Gliadel wafers for the treatment of pituitary tumors. This study demonstrated that Gliadel wafers could be safely implanted in the sella via a transcranial or transsphenoidal approach, with no complications attributed to the wafers.[67] Controlled studies will be necessary to determine if Gliadel wafers are an effective adjunct for the treatment of aggressive pituitary tumors.

PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR GAMMA AGONISTS

Peroxisome proliferator-activated receptor gamma (PPAR-γ) is a ligand-dependent transcription factor that regulates fat and glucose metabolism and has an pro-apoptotic effect through cell cycle arrest and inhibiting angiogenesis.[68] PPAR-γ activation has shown promise in vitro and in many animal models of malignancy.[69] In 2002, Heaney and colleagues[70] demonstrated PPAR-γ expression in ACTH-secreting cells in normal human pituitary and increased expression of PPAR-γ in ACTH-producing pituitary adenomas. However, in contrast with promising in vitro experiments and animal studies, positive clinical studies supporting the effect of PPAR-γ agonists in patients with pituitary tumors are lacking. A study performed in patients with acromegaly showed no effect of the PPAR-γ agonist rosiglitazone on GH or IGF-1 levels.[71] In another study, patients with Cushing disease and Nelson syndrome showed no response to rosiglitazone.[72]

OTHER TREATMENTS

BIM-23A760 is a chimera of somatostatin and dopamine, and is able to suppress both GH and prolactin. This molecule has gained interest for the treatment of both functional and nonfunctioning pituitary adenomas, as most nonfunctioning pituitary adenomas express dopamine and prolactin receptors.[73–75] In an in vitro study, BIM-23A760 was shown to induce apoptosis of nonfunctioning pituitary adenomas, likely through activation of dopamine receptors.[73] A multicenter study of nonfunctioning pituitary tumors from

patients who underwent surgery also showed inhibition of tumor growth by BIM-23A760.[76] A phase 2 clinical study with BIM-23A760 in 11 patients with acromegaly initially showed promising results with a reduction in growth hormone levels; however, subsequent data revealed less impressive somatostatinergic activity, and drug development was halted.[33]

Estrogen receptors are present on pituitary tumors, and high-dose estrogen may increase the growth of some pituitary tumors.[77] In vitro administration of an estrogen antagonist to cultures of human pituitary tumors inhibited the production of pituitary tumor transforming gene, which is involved in pituitary tumorigenesis and angiogenesis.[78] In this same study, estrogen antagonism inhibited rat pituitary tumor growth. Tamoxifen, an estrogen receptor antagonist, has been used in patients with bromocriptine-resistant prolactinomas, with reductions of prolactin levels but without clinical cure.[36]

There are other case reports and smaller studies of novel treatments for aggressive pituitary tumors. Capecitabine, a chemotherapeutic that acts via its conversion to 5-fluorouracil, has been used in combination with temozolomide in 1 case of an aggressive ACTH-producing adenoma. This chemotherapy regimen, which has been used previously for patients with other neuroendocrine tumors, was effective in temporarily reducing tumor burden in the patient.[79]

SUMMARY

The therapy of aggressive pituitary adenomas remains a challenge, and randomized clinical trials are lacking. Even with improved surgical technology and more molecular targets for medical therapy, the prognosis for patients with aggressive pituitary adenomas and carcinomas remains poor. At this time, the authors recommend multimodal therapy, careful evaluation, and individualization of treatment for each patient.

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