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Management of Refractory/ Aggressive Pituitary Adenomas Review of Current Treatment Options

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Abstract

Tumors of central nervous system (CNS) account for a small portion of tumors of human body, which includes tumors occurring in the parenchyma of brain and spinal cord as well as their coverings. This chapter covers some new development in some major brain tumors in both pediatric and adult populations, as well as some uncommon but diagnostic and management challenging tumors.

Keywords: refractory pituitary adenoma, macroadenoma and microadenoma, trans-sphenoidal adenomectomy, targeting therapy

1. Introduction

The anterior pituitary gland (adenohypophysis) is an important organ for human development and physiological functions (so called “Master Gland”), which comprises several different cell types, responsible for the synthesis and secretion of a specific hormone or group of specific hormones (plurihormonal), such as growth hormone (GH), adrenocorticotrophic hormone (ACTH), and prolactin (PRL). Each of these cell types may give rise to a discrete pituitary adenoma (PA) subtype that is either hormonal active (functional) or inactive (nonfunctional).

As one of the most common pituitary neuroendocrine tumors, pituitary adenomas (PAs) constitute the overwhelming majority of tumors arising in the pituitary gland and account for 10–15% intracranial neoplasms. Incidental microadenoma (smaller than 10 mm in diameter) may occur in up to 27% of pituitary glands examined at autopsy, and up to one-fifth of the human population has pituitary abnormalities on magnetic resonance imaging (MRI).

Majority of PAs are benign and slow growing; however, up to 10% of PAs are aggressive with invasive growth and can exhibit clinical abnormal behavior with high rates of recurrences [1]. Based on the recent WHO classification in 2017, a more detailed tumor classification by immunohistochemical stain (IHC) was proposed, which identifies a subset of PAs with aggressive clinical behavior characterized by clinical recurrence, which includes PAs with elevated Ki-67 proliferation

index, sparsely granulated somatotroph PAs, Lactotroph PAs in men, silent corticotroph PAs, Crooke cell PAs, and plurihormonal PAs with PIT-1 positivity. PIT-1 is one of the pituitary transcription factors, sometimes to be used to clarify the PAs' tumor linages.

Clinically, a subset of aggressive PAs characterized with high Ki-67 index, rapid growth, frequent recurrence, and resistant to conventional treatments is defined as refractory PAs [2]. These refractory PAs often have a very poor prognosis and even with an occasionally fatal outcome; however, there is no general agreement about how to manage the patient with refractory PAs. For neurosurgeons and clinicians, it is difficult to optimally choose the therapeutic options in treatment of refractory PAs in order to improve the prognoses of these patients; it is very important and necessary to review the emerging treatments for refractory PAs. This chapter is going to review some current treatment options for those refractory PAs.

2. Management of refractory PAs by surgical treatment

Typically, multimodal approaches are required for managing refractory PAs. Except prolactin-secreting adenomas (prolactinomas), which should be first treated with dopamine agonists (DAs), the primary treatment option is usually surgery, even surgery is usually unable to cure or control the refractory PAs [3]. However, the therapeutic goals of surgery are maximum reduction of tumor mass, decompression of visual pathways, best possible reduction of hormonal oversecretion, amelioration of clinical symptoms, and minimization of complications [4].

Most of the refractory PAs are largely invasive, infiltrating adjacent tissues; repeated surgery seldom achieves complete tumor excision. However, surgical resection is still necessary to relieve compressive symptoms [5].

Repeated trans-sphenoidal surgery is generally more difficult to perform than the initial operation due to the increased risk of morbidity and mortality. The comparison of microscopic craniectomy and endoscopic approach for recurrent or residual pituitary adenomas remains controversial.

Heringer performed a meta-analysis to evaluate effect of repeated trans-sphenoidal surgery in recurrent or residual pituitary adenomas and found that half of secreting tumors and more than half of nonfunctional pituitary adenomas (NFPAs) could achieve remission after surgery, and there is no difference between endoscopic and microscopic approach [6]. However, Esquenazi and his colleagues performed another meta-analysis to compare the effects of endoscopic and microscopic trans-sphenoidal surgery on recurrent and/or residual pituitary adenomas and found that endoscopic surgery led to modest increases in resection rates on residual or recurrent adenomas [7]. Do et al. [8] retrospectively analyzed 61 patients with recurrent or residual pituitary adenomas who underwent endoscopic endonasal surgery and found that the gross total resection was achieved in 31 patients (51.7%), indicating that endoscopic endonasal approach is a safe and effective option for recurrent pituitary adenomas. The results from another meta-analysis performed by Li also indicated that the endoscopic surgery is related to higher gross tumor removal and lower incidence of complications in patients with PA [9]. Almeida accessed the outcomes of reoperation for patients with residual or recurrent growth hormone-secreting PA from authors' institution, and no statistically significant difference was found in disease control rates between the reoperation and first-time neurosurgery. They further systematically reviewed 161 reoperations and 2189 first-time surgery cases retrieved from 29 papers and found that reoperation and first-time surgery had similar control rates for microadenomas, but the reoperation was related to substantially lower control rates for macroadenomas (27.5%) and tumors invading the

cavernous sinus (14.7%) [10]. In 2016, a systematic review and evidence-based guideline for the residual or recurrent NFPAs was produced by Congress of Neurological Surgeons, and the repeat resection is recommended as level III recommendations for the treatment of symptomatic recurrent or residual NFPAs [11].

Based on the previous studies and our experience, endoscopic surgery is better than the microscopic surgery for recurrent pituitary adenomas; however, these findings are needed to be verified by the large-scale prospective randomized controlled trials. Therefore, maximum tumor resection, meanwhile preserving nerve function is the goal to achieve local control and decompress vital structures for those refractory PAs with compressive symptoms.

3. Radiation therapy

Despite the success of trans-sphenoidal surgery or maximum tumor resection, most refractory PAs will regrow or recur; therefore, other therapeutic approaches are usually necessary. If surgical and/medical therapy failed to control the tumor growth, radiation therapy (RT) is currently the next treatment option [1]. There are several RT options for patients with refractory PAs. Fractionated external beam radiation therapy (EBRT) has been used for several decades and has shown good clinical safety and efficacy [12]. Stereotactic radiosurgery (SRS) is the delivery of a high single dose of radiation under conditions of accurate positioning. Recently, SRS has been gaining popularity due to the minimizing exposure of normal brain tissue to radiation. SRS has been preferred over fractionated photon beam because of the convenience of single day therapy and the potential for the faster effect on tumor [13]. A variety of SRS including Gamma Knife, CyberKnife, and proton-beam RT are available to deliver stereotactic RT. However, some refractory PAs are not candidates for stereotactic RT because of the tumor size (>3 cm), or tumor location near the optic apparatus and brainstem (<5 mm) [14]. Risks associated with RT include hypopituitarism, optic neuropathy, and other cranial neuropathies, which should be concerned and avoided [12].

Comparing EBRT and SRS may help to guide decision making for patients with residual or recurrent pituitary tumors. Kong et al. [15] compared the efficacy and safety of SRS and EBRT for the treatment of 125 patients with PAs. Although no significant difference was found in either biochemical remission or tumor growth control, the time to biochemical remission after SRS was much shorter than EBRT (26 months vs. 63 months).

To better understand the effects of SRS for Cushing disease (CD), Mehta et al. [16] performed an international, multicenter, retrospective cohort analysis, 278 patients with CD received SRS was retrospective cohort analyzed, and found that the overall rate of durable control of hypercortisolism was 64% for 10 years, and the adverse radiation effects included hypopituitarism (25%) and cranial neuropathy (3%) were observed.

Both conventional radiotherapy and stereotactic RT have shown a good tumoristatic effect on typical PAs; however, they may be largely ineffective and rarely maintain a long-term remission in refractory PAs. As a matter of fact, one of the aggressive PAs with high recurrent potential, silent corticotroph PAs, is with high sensitivity to radiation, so RT can be a good option for patients with those kind of PAs.

4. Medical therapy

Medical therapy plays an increasingly important role in the management of PAs. Temozolomide (TMZ), an orally administered alkylating chemotherapy, is

recommended as the first-line chemotherapy for aggressive pituitary tumors and pituitary carcinomas after the failure of standard therapies by the European Society of Endocrinology [17]. TMZ is considered the standard treatment in the management of gliomas. Since 2006, the first successful treatment of PA with TMZ was reported [18, 19], and TMZ treatment has also been widely used for patients with refractory PAs and carcinomas [20]. However, only about 50% of pituitary tumors are sensitive to TMZ treatment, and most of the refractory PAs failed to respond to TMZ and even acquired TMZ resistance after the effective response to TMZ [21]. Therefore, it is important to enhance the efficacy of TMZ and overcome the resistance of TMZ. Some molecular status of pituitary tumors, such as O⁶-methylguanine-DNA-methyltransferase MGMT and MSH6, has been associated with temozolomide response [22]. It is reported that the PI3K/AKT/mTOR signaling pathway is upregulated in pituitary tumors, and the inhibition of this pathway may enhance the TMZ-mediated cytotoxicity [23].

Epidermal growth factor receptor (EGFR) is a cell growth factor, which regulates cell proliferation and hormone production in pituitary tumors [24]. EGFR is overexpressed in prolactinoma and ACTH-secreting pituitary adenomas, which may offer a potential therapeutic target for refractory pituitary tumors [25, 26]. As an EGFR inhibitor, gefitinib has shown antiproliferative and apoptotic effects in corticotroph tumor cell *in vitro* [25]. Lapatinib, a dual HER2/EGFR inhibitor, was shown to both suppressed PRL mRNA expression and secretion more than gefitinib in animal model of prolactinomas [27].

Although further clinical trials are needed, preclinical data suggest that the EGFR pathway may be an effective therapeutic targeting for patients with refractory pituitary tumors.

Vascular endothelial growth factor (VEGF) is a potent angiogenic factor in pituitary tumors. The previous studies indicated that angiogenesis is associated with adenoma development, local invasion, and recurrences [28–30]. Several researches reported that angiogenesis decrease tumor sizes in human and experimental pituitary tumors [31–33]. Ortiz has reported the first case of a bevacizumab-treated pituitary carcinoma with long-term stabilization of disease in 2012 [34]. Touma also presented one case of pituitary carcinoma treated successfully with concurrent chemoradiation therapy and bevacizumab with a long-term follow up [35]. However, the role of anti-VEGF therapy in pituitary tumors is still controversial due to the lack of large-scale clinical trial.

Phosphatidylinositol 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) cascades is key signaling pathways in tumorigenesis of pituitary adenoma [36]. The previous studies reported that the PI3K/AKT/mTOR pathway is upregulated and overactivated in pituitary adenomas, implicating an important role in tumor formation and progression of pituitary adenoma [37–39]. Inhibition of the PI3K/mTOR signaling pathway not only displays antitumor efficacy against pituitary tumor [40, 41] but also sensitizes pituitary adenoma cells to radiotherapy and chemotherapy [23, 42]. Donovan reported one patient with pituitary carcinoma, which is refractory to multiple surgery, radiation, and chemotherapy, after the treatment with mTOR inhibitor (everolimus) and radiation, and the clinical improvement and stability >6 months were achieved [43].

As a promising therapeutic approach, cancer immunotherapy has been attracting more and more attention recently. To date, immunotherapy has been applied for the treatment of many tumors including glioma, lung cancer, melanoma, prostate cancer, and B cell lymphoma [44]. In 2007, Hazrati and his colleagues have reported one case of a prolactinoma treated successfully with immunotherapy for the first time [45]. Lu has reported that CD68+ macrophage

infiltration is associated with the pituitary adenoma size and invasiveness, indicating that immunotherapy may be useful to restrict the tumor enlargement and invasiveness [46]. Blocking the interaction between the programmed cell death (PD-1) protein and one of its ligands, programmed death ligand 1 (PD-L1) is one of the novel strategies for cancer immunotherapy. The expression of PD-L1 is positively correlated with improved responses to anti-PD-1/PD-L1 blockade in many cancers [47]. Mei reported that the expression of (PD-L1) is significantly higher in human functioning adenomas compared to nonfunctioning adenomas, suggesting the existence of an immune response to pituitary tumors [48]. Therefore, these researches raise the possibility of considering immunotherapy for the refractory PAs.

5. Conclusion

Although various treatment options are available to manage these refractory pituitary tumors, the efficacy is limited. Therefore, the new therapeutic approaches and such randomized clinical trials are needed. It is hoped that further research may clarify the tumorigenesis and pathogenesis of refractory PAs, and additional alternative treatments may be developed for these tumors in the near future.

Declaration of interest

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Abbreviations

TMZ	temozolomide
WHO	World health organization
IHC	immunohistochemical stain
ACTH	adrenocorticotrophic hormone
CD	Cushing disease
CS	Cushing's syndrome
DA	dopamine agonists
EBRT	external beam radiation therapy
EGFR	epidermal growth factor receptor
NFPA	nonfunctional pituitary adenomas
PD-L1	programmed death ligand 1
RPA	refractory pituitary adenoma
RT	radiation therapy
SRS	stereotactic radiosurgery
TSS	trans-sphenoidal surgery
VEGF	vascular endothelial growth factor

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