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REVIEW ARTICLE

Prolactinomas Resistant to Dopamine Agonists: Pathophysiology and Treatment

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Abstract

Prolactinomas are the most common functional pituitary tumors, accounting for 40% of all pituitary adenomas. Medical treatment with dopamine agonists (DA), mainly cabergoline, is considered the primary therapy for these patients. Prolactin normalization is achieved in 80–90% of prolactinomas treated with cabergoline. Patients resistant to the standard dose can escalate the dose of cabergoline up to the maximum tolerated dose. The expression of dopamine (D2) receptors and dopamine affinity is decreased in aggressive and resistant prolactinomas. Patients with aggressive and DA-resistant adenomas or with rare PRL-secreting carcinomas can be treated off-label with temozolomide (TMZ), a DNA alkylating agent. TMZ is effective in 40–50% of treated lactotroph tumors showing at least a partial response. However, patients tend to escape from the effect of TMZ after a limited time of response. Other therapeutic options include aromatase inhibitors, the somatostatin receptor ligand pasireotide, peptide receptor radionuclide therapy (PRRT), immune-checkpoint inhibitors, tyrosine-kinase inhibitors, or everolimus, the mammalian target of rapamycin inhibitor. These experimental treatments were effective in some patients carrying refractory prolactinomas showing usually partial tumor control. However, the number of treated patients with any of these new therapeutic options is very limited and treatment results are inconsistent, thus additional experience with more patients is required.

Key Words: Prolactin, Prolactinoma, Dopamine agonist, Dopamine resistance, Cabergoline, Bromocriptine.

Introduction

Prolactinomas are benign anterior pituitary adenomas composed of lactotroph cells that produce and secrete excess prolactin (PRL). These adenomas are the most common functional pituitary tumors, accounting for 40% of all pituitary adenomas. Prolactinomas are more common in females but are also diagnosed in males. Based on their size at presentation, these tumors are divided into microprolactinomas (<10 mm) frequent in women, and macroprolactinomas (≥10 mm), more frequent in men (1).

Prolactin production and release from pituitary lactotroph cells is tonically suppressed by dopamine secreted from specific neurons in the arcuate nucleus of the hypothalamus. After crossing, dopamine reaches the anterior pituitary through the hypothalamus-pituitary portal venous system, where it binds to D2 dopamine receptors (D2R) which are expressed by both, normal and tumoral lactotrophs. D2R are seven-transmembrane domain G-protein coupled receptors (2), and when activated by dopamine they suppress PRL synthesis and release and decrease cell proliferation.

Patients diagnosed with prolactinomas often present with symptoms related to hyperprolactinemia, including galactorrhea, ovarian dysfunction, amenorrhea and infertility in women, and hypogonadism in men. In addition, symptoms related to mass effect on surrounding tissues

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are frequent in patients with invasive macroadenomas, especially in men, and result in headaches, chiasmal compression, ophthalmoplegia and, occasionally, hypopituitarism (1).

Dopamine Agonists

Medical treatment with dopamine agonists(DAs) is considered the primary and "gold standard" therapy for most patients with prolactinoma, whether female or male, microadenomas and macroadenomas and intrasellar or aggressive tumors. Bromocriptine, an ergot derivative with an agonist binding to the D2R, originally marketed as Parlodel, was the first DA to demonstrate efficacy already 50 years ago. Bromocriptine has a short half-life and is administered 2–3 times a day at a daily dose of 2.5–15 mg. Bromocriptine normalized PRL in 80–90% of microprolactinomas and 70% of macroprolactinomas, with tumor shrinkage and normal gonadal function in most patients (1). Over the past 25 years, cabergoline, originally marketed as Dostinex, has become the most widely used DA worldwide. Cabergoline is a long-acting D2 receptor agonist, an ergot derivative, given to patients with prolactinoma once or twice weekly. Cabergoline is also used to treat patients with Parkinson's disease. Most prolactinoma patients achieve hormonal remission, symptom control, and adenoma shrinkage with a weekly dose of 0.5–2 mg (3). Cabergoline is considered the preferred DA for prolactinomas due to its increased efficacy, safety profile, and convenient administration schedule. Prolactin normalization is achieved in 80–90% of prolactinomas with cabergoline (4–5). With increasing adenoma size, the remission rate decreases to 70–80% in macroprolactinomas. Moreover, the shrinkage effect of macroprolactinomas is remarkable (6–7) and visual impairment improves in 70–90% of patients carrying macroadenomas with chiasmal damage. Characteristically, visual field improvement can be observed within a few days of treatment initiation.

Resistant Prolactinomas

Most patients (90%) with prolactinomas will respond to treatment with DA achieving PRL normalization and significant tumor shrinkage. In a meta-analysis that included 55 series with 3,564 patients with prolactinoma on DA treatment, 70% of patients were female, 67% had macroadenomas with a median adenoma diameter of 27.6 mm, and 86% of tumors were invasive (8). Prolactin normalization with DAs occurred in 81% of these patients. Hormonal remission was achieved in 91% of patients with microprolactinoma and 88% of patients treated with cabergoline (8). These rates were lower for macroprolactinoma (77%) and in patients with giant prolactinomas (41%). Resistance to DAs was defined as failure to normalize PRL with a continuous daily dose of 10 mg bromocriptine (the standard dose) or 2 mg/week of cabergoline (the usual maximum indicated dose) and up to the maximum tolerable dose of cabergoline (3.5 mg/week or more). In addition, inadequate reduction in the adenoma size (decrease of the maximal adenoma diameter or volume by >30 or 50%, respectively) indicates failure of DAs in patients with macroprolactinomas where tumor control is required (9). Others also suggested the absence of ovulation in females and the persistence of hypogonadism in males despite adequate treatment as an indication of resistance (10).

Most refractory adenomas show a partial response with significant PRL suppression but not normalization (PRL nadir levels >3 x upper limit of normal) (Figure 1), whereas complete resistance with no effect on PRL levels or minor hormonal suppression is rarely observed. A small number of adenomas continue to enlarge while receiving treatment with high doses of DAs. However, these tumors are rare and the underlying mechanism is unknown. Cabergoline is generally more effective than bromocriptine in suppressing PRL and decreasing tumor size (11), so patients who partially respond or do not respond at all to bromocriptine may be switched to cabergoline to achieve a better effect (12). Resistance to cabergoline may occur in men with aggressive macroadenomas, but there are also microprolactinomas that do not respond to DAs in women. Rarely, the responsiveness of a prolactinoma to DAs is selective with dissociated effects on hormone suppression or adenoma shrinkage. Lactotroph carcinomas are extremely rare and usually present as aggressive pituitary tumors resistant to DA. Secondary resistance to medical treatment is hardly found after a long-lasting hormonal response and tumor control with a DA, indicating an unusual transformation of a benign prolactinoma into a PRL-secreting metastatic carcinoma (13). Distant metastases that define carcinomas are extremely rare, but lactotroph carcinomas are the second most frequent pituitary carcinomas after ACTH-secreting pituitary carcinomas and comprise 30% of all pituitary carcinomas (14–15).

Molecular Pathophysiology

Dopamine resistance is a complex and still unclear phenomenon. Refractory adenomas, found mainly in males, tend to be large and invasive with a high proliferation rate (Ki-67 and mitotic activity) (16). The molecular mechanisms leading to dopamine resistance are uncertain, but probably include several abnormalities of the D2 receptor, affecting both quantitative expression and ligand affinity (Table 1). The expression of D2 receptors is decreased in aggressive and resistant prolactinomas compared to prolactinomas that respond to DAs (16). The change in the ratio of short to long isoforms of the dopamine D2 receptor (17) or activity of Gi/Go proteins coupled to adenylate cyclase may be related to DA resistance. Prolactin is a known physiological regulator of lactotroph function, which

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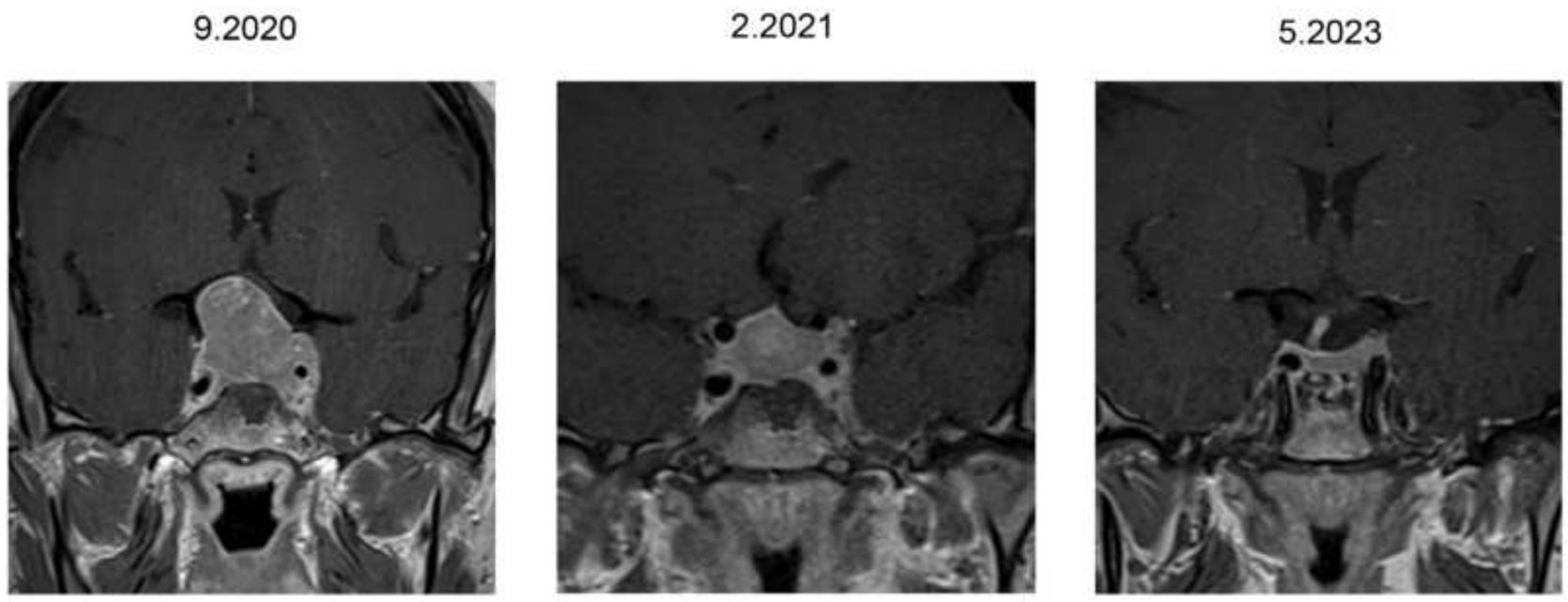

Figure 1. A 38 year-old male presented on 9/2020 with low libido, erectile dysfunction, and weight gain. Testosterone was very low, PRL measured 4,300 ng/mL (normal, below 20), and MRI showed a large and invasive macroprolactinoma compressing the optic chiasm. Visual field studies were compatible with bitemporal hemianopsia. Treatment with cabergoline was initiated and gradually escalated to 3.5 mg/week. PRL was significantly reduced but not normalized. Testosterone levels did not recover. This figure shows the massive tumor reduction after cabergoline treatment with visual field improvement and normalization.

Table 1. Clinical, histological, and molecular characteristics of refractory prolactinomas

Males, young
Large invasive macroprolactinoma
Elevated proliferation rate (Ki-67 and mitotic activity)
Decreased expression of D2 receptors
Short to long D2 dopamine receptor isoforms ratio
Activity of Gi/Go proteins coupled to adenylate cyclase
Densely granulated PIT-1 positive prolactinomas
Down-regulation of the TGFβ/Smad signalling cascade
Low ERα expression
Low Filamin-A expression.
Somatic hotspot SF3B1 mutations; Somatic POU6F2 mutation

controls PRL secretion and cellular turnover, through an autocrine/paracrine mechanism. Different variants of the PRL receptor may be associated with cabergoline resistance (18). However, inactivating mutations of the D2R have not been described and are not associated with dopamine-resistant prolactinomas (19). Down-regulation of the transforming growth factor β (TGFβ)/Smad signaling cascade was reported in DA-resistant prolactinomas, so TGFβ may be associated with dopamine resistance (20). Filamin-A is required for D2R expression and signaling in lactotrophs, and the altered response to DAs in resistant prolactinomas may be related to the reduction of filamin-A expression (21). Recently, somatic mutations in SF3B1 have been identified in 20% of subjects included in a large cohort of prolactinoma patients (22). SF3B1 is a component of the U2 small nuclear ribonucleoprotein (snRNP) complex, which has been involved in other cancer types. Mutated SF3B1 prolactinomas were associated with shorter progression-free survival and contributed to increased malignancy of some prolactinomas. Somatic mutations in the POU6F2 gene and inhibition of POU6F2 activity may contribute to the development of resistant prolactinomas (23). Normal lactotroph cells and most lactotroph tumors express estrogen receptors (ERα). Low ERα expression is more common in male lactotroph tumors and has been correlated with tumor size, invasiveness, Ki-67 index, mitotic count, dopamine resistance, and tumor progression (24). Moreover, the direct interaction between the ERα and PRL/PRLR pathways may contribute to dopamine resistance (25). Vascular endothelial growth factor (VEGF) is overexpressed in many lactotroph tumors. VEGF expression is higher in men than in women and higher in pituitary carcinomas than in benign adenomas (16). Overexpression of VEGF in prolactinomas may represent a potential therapeutic target in resistant prolactinomas.

Treatment of Dopamine-resistant Prolactinomas–the Multimodal Approach

The first step in patients with bromocriptine-resistant prolactinomas is to switch to cabergoline treatment (11–12). Patients resistant to the standard dose of cabergoline are advised to escalate and increase the dose up to the maximum tolerated dose (10). The maximum dose varies from individual to individual and can reach 10–12 mg/week (26). The weekly dose should be gradually increased every 4–6 weeks as long as the PRL levels continue to decrease after dose escalations and without adverse effects. Ono M, et al. (26) published a cohort of 150 patients with prolactinoma, including 90 subjects intolerant or resistant to DAs. They reported that a cabergoline dose of >2 mg/week was required in 20% of the patients to normalize PRL, while some patients required weekly doses of 7–12 mg. Importantly, the reduction in the size of prolactinomas is slow

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and usually takes several months after PRL suppression by DAs.

Pituitary surgery is the next therapeutic step for patients with refractory prolactinomas that require tumor control. Most patients operated for microprolactinomas or noninvasive intra-sellar macroadenomas have a high probability of achieving normprolactinemia immediately after surgery (27,28); however, relapses may occur during long-term follow-up. Patients with macroadenomas invading the cavernous sinus rarely achieve long-term hormonal control after adenoma resection. Moreover, surgical resection may also be hampered by intratumoral fibrosis that may appear after long-term DA treatment (29). Nevertheless, postoperative PRL levels may decrease drastically, and the small tumor remnant may now respond better to cabergoline treatment, occasionally with a lower dose (30).

It should be noted that not all refractory prolactinomas require additional treatment such as surgery. Maintenance with a DA is a reasonable option in patients without mass effects, in whom reduction of the adenoma is not crucial due to its location, or in patients with a controlled tumor but due to persistent hyperprolactinemia, hypogonadism continues and requires additional sex hormone replacement.

Sellar radiotherapy may be offered to patients with aggressive and refractory prolactinoma, as adjuvant therapy, preferably after cytoreductive pituitary surgery. Tumor control after gamma knife radiosurgery was evident in 17–25% of irradiated patients, with normalization of PRL and no need for DA continuation (31,32). In addition, up to 50% of the patients experience hormonal and clinical improvement after radiosurgery with persistent treatment with DAs. In a recent review by Niculescu DA et al, the published experience with radiotherapy in 428 patients with resistant prolactinoma was summarized (33). 411 patients received radiosurgery. In terms of tumor volume control, the nine included studies showed volume reduction ranging from 29–100% of patients and tumor stabilization from 23–92%. Normal PRL levels were reported in 0–63% of cases off dopaminergic treatment and in 14–100% of patients maintained on medical treatment in the different series (33). Continued treatment with DAs while the patient is undergoing radiosurgery may lead to a lower response, due to the potential radioprotective effect of DAs. Long-term follow-up after radiotherapy is recommended to identify the possible occurrence of new anterior pituitary deficits.

Most refractory prolactinomas will respond well to the multimodal approach of high-dose cabergoline treatment, debulking pituitary surgery and, if still needed, radiotherapy for the tumor remnant. This approach can effectively suppress PRL levels to normal or near normal in many patients (30), often accompanied by a significant reduction in tumor volume. However, some patients do not get enough benefit and require alternative treatments.

Temozolomide

Temozolomide (TMZ), a DNA alkylating chemotherapeutic agent that can cause base mismatches resulting in an ineffective DNA repair, is approved and administered to patients with glioblastomas. TMZ is used as off-label therapy in patients with aggressive pituitary adenomas and pituitary carcinomas including refractory prolactinomas and lactotroph carcinomas. In the cohort study of TMZ treatment of 166 aggressive pituitary tumors conducted by the European Society of Endocrinology (14), 40 cases were aggressive and refractory prolactinomas or lactotroph carcinomas. Temozolomide was effective in 40–50% of treated refractory lactotroph tumors, showing at least a partial response with an improved overall survival rate. Few patients achieved complete remission; however, drug resistance was common and recurrence rates were high. Lactotroph tumors were more likely to respond and demonstrate regression with TMZ compared with non-functioning tumors. In a subsequent survey of 171 patients with aggressive pituitary adenomas and pituitary carcinomas, including 54 lactotroph tumors, TMZ was administered to 156/171 (91%) of the cohort (15). The radiological response was reported as complete remission in 9.6% of patients; partial response in 30.1%; stable disease in 28.1% of patients; and progressive disease in 32.2%. Treatment with TMZ may be continued for at least six months in responsive patients or longer if response is maintained. TMZ is generally well tolerated, but patients may experience nausea, fatigue, leukopenia, and thrombopenia.

The use of TMZ for resistant prolactinomas is limited and is considered the last option only for aggressive or metastatic tumors, as many patients escape from the beneficial effects of TMZ after a limited period of response.

Other Experimental Therapies

The aromatase inhibitors anastrozole or letrozole combined with high-dose cabergoline were administered to men with dopamine-resistant prolactinomas and persistent hypogonadism that resulted in a significant decrease in PRL levels and adenoma reduction (34,35). Aromatization of testosterone to estrogen may be associated with the aggressive behavior of refractory prolactinomas. Thus, reduction of estrogen levels with aromatase inhibitors may lead to a decrease in estrogen-stimulated PRL secretion and increased sensitivity to DAs in resistant prolactinomas, while improving the condition of hypogonadism.

The somatostatin analog octreotide, with the recognized enhanced affinity for somatostatin receptor 2 (SSTR2), does not usually affect PRL release from prolactinomas (36). However, the addition of octreotide to ongoing treatment with cabergoline may be partially effective in some patients with dopamine-resistant macroprolactinoma as reported by Sosa-Eroza E, et al. (37). Pasireotide is

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a somatostatin receptor ligand with an increased affinity for SSTR5, approved for the treatment of acromegaly and Cushing's disease. SSTR5 expression is uncommon in prolactinomas; however, few cases of dopamine-resistant prolactinomas successfully treated with pasireotide have been described, with normalization of prolactin and tumor size reduction (38,39).

Peptide receptor radionuclide therapy (PRRT) with Lu^{177}-DOTA-TATE, $Yttrium^{90}$-DOTA-TOC, or In^{111}-DTPA-octreotide, used successfully to treat GEP neuroendocrine tumors (NETs), was administered to a few patients with aggressive prolactinomas after the failure of conventional multimodality treatment, with tumor control in approximately one-third of the patients (40,41). However, Burman P, et al. in the large survey of aggressive and refractory pituitary tumors (15) were not able to show comparable treatment success in five patients treated with PRRT for refractory lactotroph adenomas. PRRT treatment was safe in most patients, but at present, considering the limited experience, PRRT should be considered for refractory prolactinomas only in an experimental setting.

Everolimus, the mammalian target of rapamycin (mTOR) inhibitor, is approved for the treatment of NETs. The mTOR pathway was shown to be activated in refractory prolactinomas and everolimus exhibited antiproliferative actions when added to cabergoline, resulting in decreased PRL levels and tumor regression (42,43).

Treatment with the immune-checkpoint inhibitors ipilimumab and nivolumab was administered to a small number of patients with aggressive lactotroph adenomas and lactotroph carcinomas. Half of the treated lactotroph tumors showed at least partial radiological response (44,45). Therefore, checkpoint inhibitors are a promising therapeutic option after temozolomide failure and should be investigated in patients with refractory and aggressive lactotroph tumors.

Burman P, et al. reported on five patients with refractory lactotroph adenomas and carcinomas who were treated with bevacizumab, an anti-VEGF treatment, in combination with or after failed TMZ therapy. Besides one patient who showed stable disease, all the others progressed (15).

Lapatinib, a tyrosine-kinase inhibitor directed against EGFR and erbB2 tyrosine-kinase, inhibited PRL secretion and reduced tumor volume in two patients with prolactinomas resistant to high-dose cabergoline (46). In a phase 2a trial, three out of four participants with refractory aggressive prolactinomas showed stable disease with tumor control but no PRL suppression (47).

Summary

Most DA-resistant lactotroph tumors will respond to a combined treatment approach that includes high-dose cabergoline, pituitary surgery, and sellar radiosurgery for adenoma remnants if identified. The use of TMZ for resistant prolactinomas is limited and is considered the last option for aggressive or metastatic tumors. Experience with new experimental therapies is limited, but some patients with refractory prolactinomas may benefit from the use of pasireotide, or certain types of inhibitors whether the immune checkpoint, the tyrosine-kinase, or the aromatase ones.

Declaration of Competing Interest

I. Shimon has nothing to disclose.

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