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Management of Dopamine Agonist-Resistant Prolactinoma

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Keywords
Pituitary tumor · Prolactin · Prolactinoma · Dopamine agonists · Therapy

Abstract
Dopamine agonists are usually very effective in the treatment of prolactinomas. Nonetheless, a subset of individuals does not respond satisfactorily to these agents, and this resistance is characterized by failure to achieve normoprolactinemia and a 30% or more reduction in maximal tumor diameter (in the case of macroprolactinoma) under maximally tolerated doses. The overall prevalence of dopamine agonist resistance is 20–30% for bromocriptine (BRC) and around 10% for cabergoline (CAB). The 2 main predictive factors are male gender and tumor invasiveness. The management of drug-resistant prolactinomas includes several options. Any BRC-resistant patient should be switched to CAB which will normalize prolactin in 80% of patients. As long as adverse effects do not develop, dose escalation of CAB is reasonable, with the expectation that subsequent dose reduction will be possible. Echocardiographic monitoring is advised in such patients because of the potential association with cardiac valvular fibrosis. Also, maintaining maximal CAB doses at 3.5 mg/week may lead to progressive hormonal control in a significant proportion of patients. Complete resistance to CAB is infrequent. In a study of 122 patients with a macroprolactinoma, only 7 (6%) could not achieve control despite maximal CAB doses for >12 months. A large resistant prolactinoma is also an indication for transsphenoidal neurosurgery, aiming at a debulking which may improve postoperative medical control. For patients who harbor aggressive prolactinomas, radiotherapy may be considered. However, normal prolactinemia will eventually occur in only one-third of patients after many years. Finally, temozolomide may be a therapeutic option in malignant/aggressive prolactinomas.

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Introduction

Drug resistance may be defined as the inability of an adequate drug, given at efficient doses, to reach therapeutic targets in a patient who shows both good tolerance and good compliance with the treatment. It is a relative concept, and a whole spectrum may exist from full sensitivity to complete resistance to the effects of the medication. It is also highly dependent on the assigned goals of therapy, which may be more or less stringent. Therefore, the definition and frequency of any drug resistance often vary widely among clinical studies and investigators. Regarding dopamine agonist (DA) treatment of prolactinomas, results may also vary depending on whether antihormonal or antitumoral effects are considered.

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The main aspects of the modern management of prolactinomas, which are or become resistant to DAs, will be reviewed here. Evidence acquisition was first made using a PubMed® search that included the terms "prolactinoma" and "dopamine agonist treatment" or "dopamine agonist resistance." On many occasions, previously published reviews dealing with the topic were used to summarize the existing literature. However, it is worth stating that this paper is not intended to be a systematic review on the subject, and, therefore, the bibliography used is not exhaustive but the author's own choice.

Prolactinomas account for approximately 50% of all pituitary adenomas coming to medical attention [1, 2] and are an important cause of hypogonadism and infertility. Medical therapy with DAs is highly effective in the majority of cases, allowing prolactin normalization and restoration of eugonadism [3], though such goals may appear unrealistic in the cases of large invasive adenomas, in which rapid reduction of tumor size and alleviation of compression are rather considered as priority endpoints [4, 5].

A subset of individuals with prolactinomas will exhibit a varying degree of resistance to DAs [6–8]. Some patients may respond poorly to one DA but well to another. Infrequently, individuals may respond well initially and later become drug resistant [8, 9]. Also, while normalization of prolactin levels achieved with a DA is most commonly accompanied by substantial tumor size reduction, cases of "selective" resistance have been reported in a few patients in whom the drug induces discordant prolactin-lowering and tumor size-reducing effects [10].

Definition and Prevalence of Resistance to DAs

There is still no universal consensus on the definition of DA resistance. Regarding hormonal response, several criteria have been used in the past, including failure to normalize prolactin levels, failure to reduce prolactin levels sufficiently to achieve ovulation, or failure to enable a 50% reduction of hyperprolactinemia [11–14]. However, as the threshold of prolactin reduction required to allow restoration of a normal gonadal axis varies on an individual basis, it seems wise to define hormonal resistance to DAs as the failure to achieve normoprolactinemia.

In the case of macroprolactinoma, resistance to DAs may also be considered when drug therapy has no or little impact on tumor size. Obviously, the frequency of this outcome is dependent on the threshold set as "significant reduction" in tumor size. Several criteria also have been used in the literature, including changes in maximal tumor diameter, height, surface, or volume, and favorable responses have been reported in terms of percentages ranging from 25 to 80% shrinkage. As the risk of compression mainly depends on tumoral extension to the optic chiasm, an appropriate criterion of tumoral response appears to be a >30% reduction in tumor height or a >50% decrease in coronal surface [15]. We acknowledge, however, that these definitions – though simple – remain arbitrary.

There is also no strict rule as to which level the dose of a specific DA should be uptitrated before classifying a patient as resistant. Most often, and taking into consideration accepted dose equivalences between the several DAs, these doses are usually defined as ≥15 mg of bromocriptine per day, ≥2.0 mg of cabergoline per week, and ≥225 μg of quinagolide per day [13, 16, 17]. Even though the intensity of the effort to increase the dose might play a role in the magnitude of the response, in most macroprolactinomas, intensive treatment with cabergoline is not superior to the conventional recommended dosage schedule in determining the time necessary to achieve normoprolactinemia and a >50% shrinkage in tumor surface [18].

When resistance to DAs is defined as (1) the failure to achieve normoprolactinemia under maximally tolerated doses of DA for at least 3–6 months, together with (2) the lack of a 30% or more reduction in tumor diameter in case of macroprolactinoma, its frequency still varies according to the type of drug and size of the tumor. Resistance is uncommonly encountered in microprolactinomas [7], is more frequent in cases of macroprolactinomas [16], and even more prevalent in giant invasive tumors [5, 19]. The estimated prevalence of resistant prolactinomas is approximately 20–30% for bromocriptine [6–8]. It is definitely lower for cabergoline, which remains so far the most powerful drug in this indication [6–8, 10–12, 20].

An overview of the efficacy of cabergoline on prolactin concentrations and tumor size is shown in Table 1 for micro- and macroprolactinomas, respectively. Overall, hormonal resistance to cabergoline is observed in <10% of microprolactinomas and in 15–20% of macroprolactinomas. These figures are, however, likely overestimated, as cabergoline administration was not always given at a sufficient dose and for a sufficient period of time. Resistance to quinagolide is more difficult to ascertain, since there are no large published series in which quinagolide was given to totally drug-naïve patients. In a meta-analysis comparing the effects of bromocriptine and quinagolide on hyperprolactinemia, there was no significant difference between both drugs [20], although it has been reported that quinagolide may overcome resistance to bromocriptine in a substantial proportion of subjects [21].

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Table 1. Overview of the efficacy of cabergoline on prolactin concentrations and tumor size in patients with micro- and macroprolactinomas

First author	Year	Ref.	Micro-adenomas	PRL normalization	Tumor reduction	Macro-adenomas	PRL normalization	Tumor reduction[a]
Webster	1993	64	100	86/100	na	1	1/1	na
Webster	1994	35	223	185/223	na	0	–	–
Biller	1996	65	0	–	–	15	11/15	11/15
Colao	1997	37	0	–	–	23	19/23	14/23
Ferrari	1997	66	0	–	–	85	52/85	41/62
Muratori	1997	67	26	25/26	13/19	0	–	–
Verhelst	1999	36	174	162/174	na	181	139/181	na
Cannavò S	1999	68	26	23/26	na	11	11/11	na
George	2000	69	0	–	–	9	7/9	3/9
Colao	2000	70	0	–	–	110	98/110	61/110
Di Sarno	2000	71	23	22/23	8/23	16	14/16	9/16
Di Sarno	2001	13	60	54/60	51/60	56	46/56	47/56
Ono	2008	39	93	93/93	na	57	56/57	na
Delgrange	2009	16	0	–	–	122	115/122	98/119
Rastogi	2013	18	0	–	–	38	33/38	36/38
Overall effects				650/725 (90%)	72/102 (71%)		602/724 (83%)	320/448 (71%)

Data retrieved from a nonexhaustive list of studies distinctly evaluating the effects of cabergoline on micro- and macroprolactinomas; data from patients with nontumoral hyperprolactinemia are not included. PRL, prolactin; na, data not available. [a] Significant tumor reduction is usually considered as a more than 30% decrease in tumor height or a more than 50% decrease in tumor coronal surface.

Full resistance to cabergoline is rare. In a study of 122 patients with a macroprolactinoma, 96 (79%) achieved normal prolactin levels with standard doses of cabergoline (0.5–1.5 mg/week), 19 (15%) required higher doses (2.0–7.0 mg/week), and only 7 (6%) could not achieve medical control despite increasing the doses to at least 3.5 mg/week [16]. Regarding giant prolactinomas, data on the efficacy of primary medical therapy have been recently reviewed [5]. Of 97 patients reported in these series and who were treated with either bromocriptine or cabergoline, 58 (60%) achieved a normal prolactin level, and in the 40% of patients who did not normalize prolactin levels with medical therapy, significant partial responses were usually observed. Moreover, a >30% reduction in maximal tumor diameter was observed in 65 (74%) of 88 patients with a giant prolactinoma [5].

Mechanisms of DA Resistance

Cellular mechanisms leading to prolactinoma resistance to DAs have been reviewed extensively [6] and are not the main focus of this review. These mechanisms likely involve several different molecular alterations which may coexist within the same tumor. In many – but not all – prolactinomas, DA resistance is associated with a reduction in subtype 2 dopamine receptor (D_2R) expression but not altered binding affinity [11, 22]. The long active isoform of the D_2R seems particularly involved [23].

However, additional molecular alterations downstream of the D_2R might also contribute to insensitivity to inhibitory dopaminergic influence. These alterations in dopamine signaling may include a reduction in mRNA levels of the inhibitory G protein alpha subunit [24], alterations in the cytoskeleton protein filamin A [25], or disruption in autocrine growth factor signaling mediated either by the tyrosine kinase receptor ErbB3 [26] or by the nerve growth factor receptor which modulates D_2R expression [27].

Among other molecular pathways involved in the pathogenesis of prolactinomas, the transforming growth factor beta-1 (TGFβ1) system has also been identified as a potential player in the induction of DA resistance and, thus, represents a putative target for the development of new treatments [28]. Briefly, TGFβ1 partially mediates the inhibitory effects of dopamine on prolactin secretion and lactotroph proliferation [29], and in turn dopamine

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and estrogens respectively up- and downregulate the pituitary expression of active TGFβ1 and its receptor [30]. Interestingly enough, a significant reduction of TGFβ1 and of its downstream intracellular effectors Smad2 and Smad3 has been recently reported in human DA-resistant prolactinomas [31].

Clinical Characteristics of Patients with a Resistant Prolactinoma

In an international multi-center study, Vroonen et al. [32] have reviewed the clinical characteristics of 92 DA-resistant patients who did not normalize their prolactin levels with cabergoline doses up to 1.5 mg/week. They found a relatively high prevalence of male patients (45%), large tumors (67% of macroprolactinomas and 16% of giant adenomas), and invasive prolactinomas (52%). The proportion of patients with a genetic predisposition to develop pituitary tumors (12/92 with a MEN1 or AIP mutation) was also increased in comparison with the general population of prolactinoma patients. In another study, Delgrange et al. [16] compared "sensitive" (prolactin normalization with a cabergoline dose <2.0 mg/week; $n = 96$) and resistant patients (no prolactin normalization or normalization with a cabergoline dose ≥2.0 mg/week; $n = 26$) and also found significant differences in the sex ratio (33 vs. 69% of men in the sensitive and resistant subgroups, respectively), in median prolactin concentration (818 vs. 4,316 μg/L) and tumor height (18 ± 1 vs. 29 ± 6 mm), and in the proportion of invasive prolactinomas (9 vs. 46%). In the same study, the authors showed that male gender and cavernous sinus invasion were the 2 factors independently associated with cabergoline resistance.

Other characteristics which have been associated with drug resistance are a very young age and cystic tumors. Prolactinomas diagnosed in children and adolescents are more often large invasive tumors, and about 25% of them do not normalize their prolactin concentrations under maximally tolerated doses of DAs [33]. Factors associated with a poor response to medical treatment were younger age, male gender, invasion, and the presence of a MEN1 mutation. On the other hand, in a recent study performed by Faje et al. [34] in 22 patients with a predominantly cystic prolactinoma, 4 patients (18%) remained hyperprolactinemic under DA and 11 of them (50%) did not achieve a >80% reduction in tumor volume (which more or less corresponds to a 50% reduction in diameter).

Management of Patients with a Resistant Prolactinoma

Several lines of treatment optimization may be considered in resistant patients: shift to cabergoline if the patient is treated with bromocriptine or quinagolide, dose escalation of cabergoline to the maximally tolerated dose, dose escalation to 3.5 mg cabergoline/week and waiting, surgical debulking, radiotherapy, or temozolomide in case of a very aggressive tumor. These options will be briefly reviewed.

Shift to Cabergoline

Of all DAs, cabergoline has been shown to be the most effective in normalizing prolactin levels [6–8, 35]. Approximately 80% of bromocriptine-resistant patients achieve a normal prolactin level using cabergoline [36, 37]. Among 20 patients resistant to both bromocriptine and quinagolide, 17 (85%) responded to cabergoline with a normalization of prolactin levels, and 70% responded with some change in tumor size [37]. In agreement with these results, a subgroup analysis from a large study of patients treated with cabergoline found that 70% of 58 patients in whom bromocriptine failed to normalize prolactin were controlled with cabergoline [36]. Of note, these patients required higher doses of cabergoline (1.5 mg/week) compared to the overall cohort (0.5 mg/week). Only 7 patients (2% of the whole cohort) were "resistant to cabergoline" as defined by a <50% decrease in prolactin levels. Two large, prospective randomized studies directly compared bromocriptine to cabergoline with respect to drug efficacy, thus allowing a comparison of the prevalence of resistance to each drug within the same study. In a large collaborative study, prolactin was normalized in 138 of the 236 (59%) women taking bromocriptine and in 186 of the 223 (83%) women taking cabergoline [35]. In a multicenter study conducted in France, 27 of 58 (48%) women taking bromocriptine and 56 of 60 (93%) women taking cabergoline normalized prolactin levels [38].

Cabergoline Dose Escalation

Partial resistance to DAs can often be overcome by increasing the dose of cabergoline stepwise to maximal tolerable doses. In a study of 150 previously untreated patients (28 men, 57 macroadenomas), Ono et al. [39] reported normalization of prolactin in all but one, with weekly doses of cabergoline >2 mg/week in 11 (4 patients required 3 mg, 2 required 6 mg, 4 required 9 mg, and 1 patient required 12 mg). Doses of cabergoline up to 21 mg/week have been reported in some very resistant cases

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[40]. As long as adverse effects do not develop, dose escalation remains indeed a therapeutic option, but patients must be informed of the potential long-term side effects of cabergoline at such high doses, in particular of the risk of cardiac valvular or pleural fibrosis, which has been reported in Parkinson patients taking very large doses of cabergoline [41]. It is also advised to attempt a dose reduction after prolactin normalization has been obtained, as this strategy may maintain a good hormonal control in most cases [42]. It must also be noted that some studies have shown little benefit to further increase the cabergoline dose beyond 3.5 mg per week, which is often considered as the maximally effective dose [6, 13].

Given these last observations, maintaining "maximal" doses of cabergoline at 3.5 mg/week and waiting for time effects may also be an efficient option, leading to hormonal control after several months in a substantial proportion of initially resistant patients [16].

Surgery

Patients partially resistant to medical treatment and who require higher than standard doses of cabergoline may also benefit from neurosurgery, even though tumor resection is incomplete. Surgical debulking of prolactinomas may indeed improve hormonal control with normalization of prolactin levels with lower postoperative doses of cabergoline [32, 43].

The transsphenoidal microscopic or endoscopic approaches represent the standard of care for all microprolactinomas and the overwhelming majority of macroprolactinomas [44]. Craniotomy may, however, be required for some giant tumors with intracranial extensions, such as those extending towards the frontal or temporal lobes [5]. Obviously, such invasive prolactinomas cannot be cured by surgery, regardless of the surgical technique employed or experience of the neurosurgeon, and it will not always be possible to normalize prolactin concentrations. However, as already mentioned, the main goals of therapy in such circumstances are to alleviate symptoms and to prevent complications related to mass effects.

Radiotherapy

Although much less employed than in the past, radiation therapy (RT) may still be a last resort option for patients who are resistant to medical therapy, have failed surgical treatment, and who exhibit an aggressive and growing or threatening prolactinoma [3]. Radiotherapy may quite efficiently control tumor growth, but it will often require many years before achieving maximal antisecretory effects, and normalization of hyperprolactinemia occurs in only one-third of the cases [7]. Several methodologies for delivery of RT are available. When used following noncurative surgery, both conventional fractionated RT and stereotaxic radiosurgery allow normalization of prolactin levels at similar rates in 20–40% of patients after a median delay of 3–10 years [45]. With the addition of medical therapy, prolactin normalization may be finally obtained in 80–90% of patients [45, 46].

Temozolomide

Temozolomide is an oral alkylating agent highly effective in pituitary aggressive neuroendocrine tumors and carcinomas, including prolactin-secreting tumors [47–49]. So far, long-term results of temozolomide treatment have been reported in 15 cases of malignant prolactinomas, with a complete response in 2 patients and a partial response in 7 (data reviewed in [45]). In responders, primary tumor volume, size of metastases, and prolactin levels were significantly reduced, although not completely normalized.

Other Available Options

In some cases (older males or postmenopausal women with no symptoms and no threat of tumoral compression or complication), close follow-up of resistant patients may be considered without necessarily normalizing prolactin concentrations [3, 7]. Hypogonadism may be treated with sex hormone replacement therapy, bearing in mind that both estrogens and androgens may contribute to an increase in prolactin concentrations despite sustained DA therapy [7, 40]. If fertility is a major concern, induction of ovulation is possible in hyperprolactinemic patients, using clomiphene citrate, gonadotropins, or pulsatile GnRH [50]. However, the planning of a pregnancy in a young drug-resistant woman with a macroprolactinoma must take into consideration the possible risk of tumor growth during gestation, which occurs in about 30% of cases if the tumor has not been reduced in size by previous medical and/or surgical treatment [51].

Estrogen receptor antagonism has been attempted in the past with little success. Thus, tamoxifen treatment of patients with a bromocriptine-resistant prolactinoma induced only a moderate reduction of prolactin concentrations [52]. More recently, Gao et al. [53] reported some prolactin-reducing effects of fulvestrant, a new estrogen receptor antagonist, in pituitary cell lines and in a murine rat model, but it is still unknown whether this compound will be able to reverse DA resistance in human prolactinomas. Interestingly enough, in a very few cases of males with resistant macroprolactinoma and hypogonadism,

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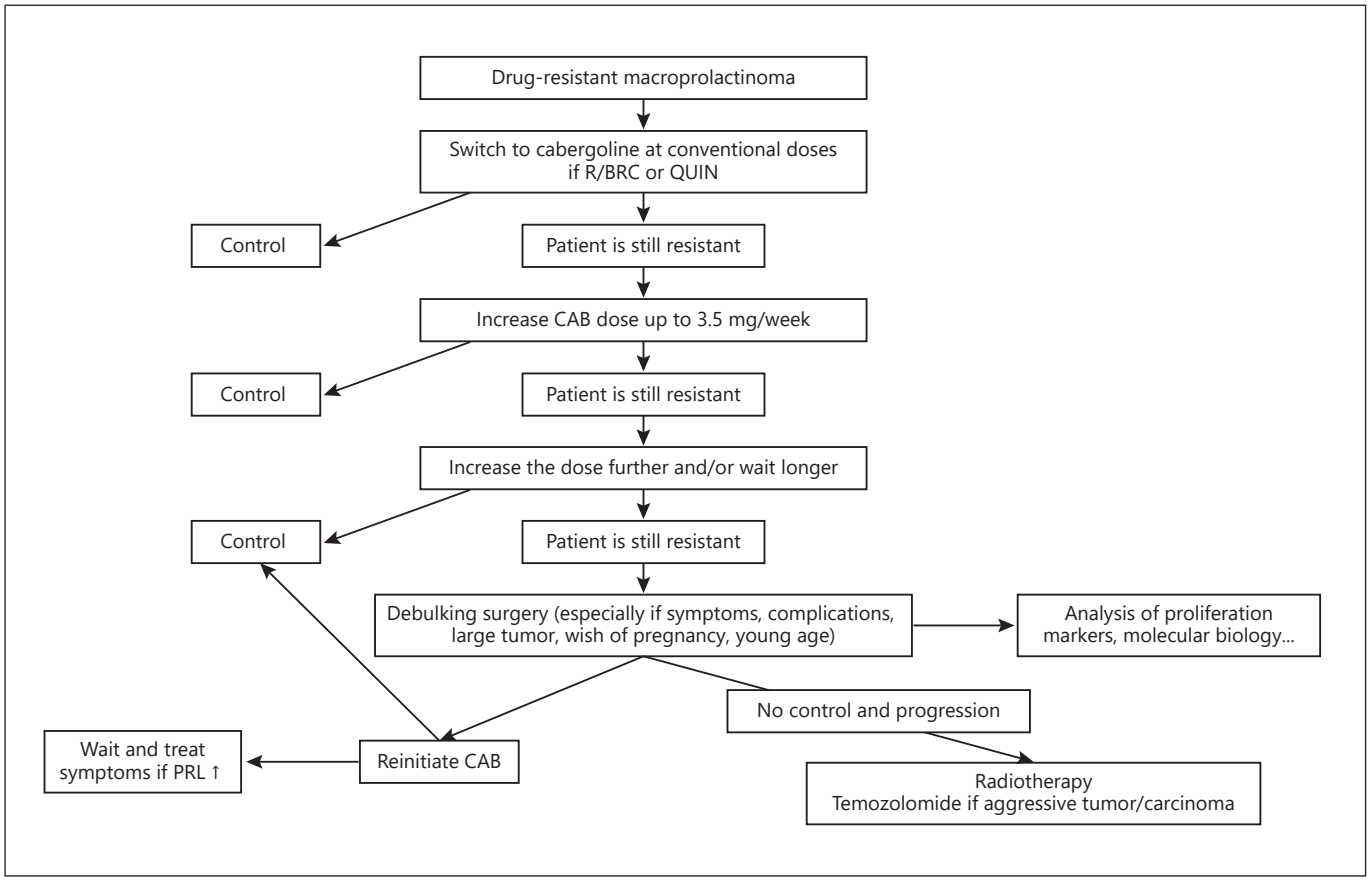

Fig. 1. Treatment strategy proposed in the case of a resistant macroprolactinoma. BRC, bromocriptine; QUIN, quinagolide; CAB, cabergoline; PRL, prolactin.

testosterone supplementation was shown to further increase drug resistance, and the use of anastrozole, an aromatase inhibitor, allowed a significant reduction of prolactin concentrations with lower doses of cabergoline [40, 54, 55]. Although a suppression of aromatase-induced estrogen conversion from testosterone was logically postulated, the mechanisms of such effects remain largely unclear, as male prolactinomas exhibit lower estrogen receptor expression than female tumors, and this downregulation is further related to a higher tumor grade, resistance to treatment, and an overall worse prognosis [56].

Future Potential Therapeutic Options

Predicting and managing resistance of prolactinomas to DAs remains a challenge, and the molecular mechanisms are complex, likely involving multiple pathways beyond the D_2R. Identification of new molecular markers highly expressed or downregulated in these resistant, often aggressive tumors should help to better understand their peculiar behavior [57, 58] and to find new therapeutic modalities, such as drugs interfering with angiogenesis or cell proliferation.

An example of such a strategy is the observation of the specific expression of several subtypes of ErbB receptors in prolactinomas, variably associated with tumor invasion and response to DAs [59]. Thus, targeting ErbB receptors might be a future effective therapy in patients with large aggressive prolactinomas. Fukuoka et al. [60] have demonstrated a suppressive effect of lapatinib, a tyrosine kinase inhibitor, on prolactin-secreting tumors in rats and on prolactin mRNA expression and secretion in human prolactinoma cell cultures in vitro. Cooper et al. [59] were the first to report in a pilot study a beneficial effect of lapatinib on prolactin levels and tumor volumes in 2 subjects with macroprolactinomas that were resistant to high doses of cabergoline.

A high expression of somatostatin receptor subtypes 2 and 5 has also been shown in some resistant prolactino-

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mas and might be correlated with a good response to a therapy combining cabergoline and octreotide [61]. In addition, the effectiveness of peptide receptor radionuclide therapy with 111-indium DTPA octreotide has been reported in a patient bearing a giant cabergoline- and octreotide-resistant prolactinoma [62]. It is, however, fair to say that most resistant prolactinomas will not respond to currently available somatostatin analogs.

As the TGFβ1 system appears to be involved in the dopaminergic inhibition of lactotroph function and growth, and TGFβ1 is downregulated in prolactinomas, and even more so in resistant prolactinomas [31], treatments that would increase the activity of the pituitary TGFβ1 circuit may represent a future attractive approach to overcome resistance to DA. Indeed, it was recently shown that in vivo administration of several analogs of thrombospondin 1 (TSP1), a natural TGFβ1 activator, was able to counteract the development of estradiol-induced prolactinomas in rats [28].

A final anecdotal – but perhaps promising – observation comes from the work of Lin et al. [63], who showed that chloroquine, a blocker of autophagic flux, may enhance suppression of cell proliferation by cabergoline, both in vitro in rat pituitary tumor cell lines and human pituitary tumor cell primary cultures, and in in vivo xenograft models in nude mice and estrogen-induced rat prolactinomas. Whether such an effect may be transposed to the treatment of human drug-resistant prolactinomas is currently unknown.

Conclusions

Most prolactinomas respond very well to low doses of DAs, but a subset of individuals shows partial or complete resistance to medical treatment. When resistance to DAs is defined as the failure to achieve normoprolactinemia under maximally tolerated doses of DA, together with the lack of a 30% or more reduction in tumor height in case of macroprolactinoma, the estimated prevalence of resistant prolactinomas is approximately 20–30% for bromocriptine and 10% for cabergoline. The 2 main predictive factors for DA resistance are invasiveness of the tumor and male gender.

The management of drug-resistant macroprolactinomas remains today challenging but includes several options which have been reviewed in this article: switch from bromocriptine or quinagolide to the more potent cabergoline, dose escalation up to maximal tolerated doses of the DA, waiting for long-term effects of medical therapy in the absence of immediate threat or complication, surgical debulking of the tumor which may improve postoperative medical control, radiotherapy in well-defined progressing cases, and temozolomide in malignant/aggressive prolactinomas. Based on these possibilities, a comprehensive treatment strategy is depicted in Figure 1.

Despite all these options, a few patients will remain hyperprolactinemic. Conservative management may be considered in such patients, provided that they have little symptoms and no serious complications. Future treatments should aim at upregulating or bypassing the D_2R and at repressing (or activating) downstream pathways involved either in prolactin secretion or cell proliferation.

Statement of Ethics

The author has no ethical conflict to disclose.

Disclosure Statement

The author has no conflict of interest to declare.

Note Added in Proof

In a recent report by Lasolle et al. [72], monotherapy with the multireceptor-targeted somatostatin receptor (SSTR) ligand pasireotide was shown to normalize prolactin concentrations and restore normal cycles in a 41-year-old woman presenting with a long-standing DA-resistant macroprolactinoma. Interestingly enough, the tumor (which had been previously operated twice) showed high SSTR5 and low SSTR2 expression.

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