

# Medical Therapies in Prolactinomas Patients Resistant to Bromocriptine

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**Abstract.** Prolactinoma is the most common pituitary tumor. Bromocriptine(BRC) is a dopamine receptor agonist(DAs), which is one of the medical treatments for prolactinomas. However, about a quarter of patients are resistant to BRC. The aim of this article is to explore medical treatment for prolactinoma patients who are resistant to BRC, including increasing the dose of BRC and substituting drugs (cabagoline, temozolomide). Since prolactinomas is predominantly microadenoma, medical therapy based on DAs is the first-line treatment. Cabergoline (CAB), belong to DAs, is progressively substituted for BRC because of its excellent tolerability and better efficacy. In addition, small percentage of patients with prolactinomas are aggressive, this means that they are naturally resistant to DAs. High doses of CAB and standard doses of TMZ are treatments for aggressive prolactinoma, however, the use of high-dose CAB has been linked to an increased risk of cardiac valvopathy in patients with both Parkinson's disease and prolactinoma. Hence, TMZ, last conservative treatment, is recommended for this subset of patients.

**Keywords:** Prolactinomas, Tumor, Bromocriptine, Clinical Therapy.

## 1. Introduction

Prolactinomas is a common pituitary neuroendocrine tumor (PitNETs) caused by excessive secretion of prolactin (PRL) from pituitary prolactinoma, accounting for half of pituitary tumors [1-3]. It mainly causes endocrine symptoms such as hyperprolactinemia (HPRL) and symptoms caused by tumor compression. Clinical manifestations were mainly divided into female menopause and non-lactation caused by increased serum PRL, and male sexual dysfunction, with a male-female ratio of 1:10. Prolactinomas are mainly microadenomas. Since men have no early symptoms, their tumors are more likely to be aggressive and macroadenomas. At present, medical therapy rather than surgery is the preferred way, and DAs are the suggested and first line therapy [1-4]. BRC and CAB among the most commonly used agents of it. Tumor aggressiveness and macroadenoma are positively correlated with DAs resistance, and most prolactinomas with DAs-resistant belong to macroadenomas [5, 6].

Researchers have found that about 10-20% of patients are resistant to DAs, among which about 25% are resistant to BRC and 15% are resistant to CAB. Both of them have similar side effects, such as nausea, dizzy and vomiting [5]. When patients with prolactinomas are treated with standard doses of DAs (BRC 7.5mg/d or CAB 2.0mg/w) in a normal patient, the concentration of PRL in serum does not recover to normal levels, and the tumor volume does not decrease to half of previous size, the patient has dopamine receptor agonist resistance [6, 7]. If this kind of patients are treated according to the dose and program of ordinary patients, the treatment cycle is longer, and the effect is worse, even the effect is slight. This article will discuss the alternative medical treatment for patients with BRC resistance, and analyzes the advantages and disadvantages of each program.

## 2. Mechanisms of BRC resistance

BRC is one of the most commonly used DAs. The molecular mechanisms of DAs resistance have not been completely found. It is well recognized that the molecular mechanism of DAs mainly involves the pathways that relate to dopamine D2 receptor (DRD2) in prolactinomas [5]. BRC can exert therapeutic effect by activating DRD2 and antagonizing DRD1 [8, 9]. In contrast, drug-resistant

prolactinomas cells usually express lower amounts of DRD2 that undermining the efficacy of the BRC [4, 6, 10]. The apoptosis of prolactinomas cells induced by DAs primarily depends on the expression of DRD2 [9]. In addition, there was research have confirmed that DRD2 expression is different between drug-resistant and sensitive prolactinomas, and between aggressive and non-aggressive prolactinomas, respectively [10]. Therefore, tumor shrinkage and reduction of PRL levels are different in drug-sensitive and drug-resistant patients with the same drug (Table 1) [5].

**Table 1.** Tumor size and PRL levels in drug-sensitive and drug-resistant patients with CAB [5]

|                         | Responders (sensitive) | Non-responders (resistant) |
|-------------------------|------------------------|----------------------------|
| Serum PRL levels(ng/mL) | 38-2600                | 72-9910                    |
| Tumor size              | 43:57                  | 13:87                      |

## 2.1. Lack of DRD2 or DRD2 reduction affects downstream signal pathways

A decrease in DRD2 will lead to a reduction in receptor density and binding sites, thereby affecting downstream signaling pathways [1, 5].

Decreased activity of transforming growth factor (TGF- $\beta$ 1) downstream of DAs is one of the signs of prolactinomas deterioration [9]. TGF- $\beta$ 1 signal pathway can inhibit PRL synthesis and secretion. When TGF- $\beta$ 1 signal pathway is inhibited, expression of related proteins and fibrosis of prolactinomas increase, resulting in DAs resistance [2, 3, 11, 12].

The imbalance of ERK (extracellular regulated protein kinase) in PI3K (intracellular phosphatidylinositol kinase) signal pathway disrupts the homeostasis of prolactinomas cells, leading to an increase in PRL secretion, activation of proliferation, migration and differentiation of prolactinomas cells, result in corresponding decrease in the sensitivity of prolactinomas to DAs [13]. In addition, PI3K is one of the dominating pathways of autophagy regulatory, which makes it difficult for BRC-resistant patients to trigger autophagy in prolactinoma cells [9].

## 2.2. Reduction of PGAM5 and CypD signaling molecules

Recent studies have found that, the reduction of prolactinomas size induced by BRC, is not only related to apoptosis, but also connected with the protein signal of necroptosis in prolactinomas. Damage and swelling of a large number of mitochondria are the symbol of prolactinomas necroptosis [8].

Necroptosis promotion by BRC that mediated by the PGAM5 (phosphoglycerate mutase family 5) -CYPD (cyclophilin D) signal pathway in prolactinomas cells by inducing RIP3 (receptor-interacting protein kinase 3) and pMLKL (phosphorylated mixed lineage kinase domain-like protein) expression [14]. These two signal proteins are both important components of necrotic death complex (necrosome) that eventually leads to necroptosis [15].

PGAM5 and CypD are proteins which related to mitochondrial metabolism, which can mediate mitochondrial swelling and rupture and eventually lead to necroptosis [16]. The decreased expression of PGAM5 and CypD can significantly inhibit the programmed necrosis of tumor cells induced by BRC [14]. However, there is almost no expression of PGAM5 and CypD in prolactinomas cell, thus, necroptosis is inhibited, and tumors are prone to proliferation and metastasis [14].

## 2.3. High expression of estrogen receptor and inhibition of AMPK signal pathway

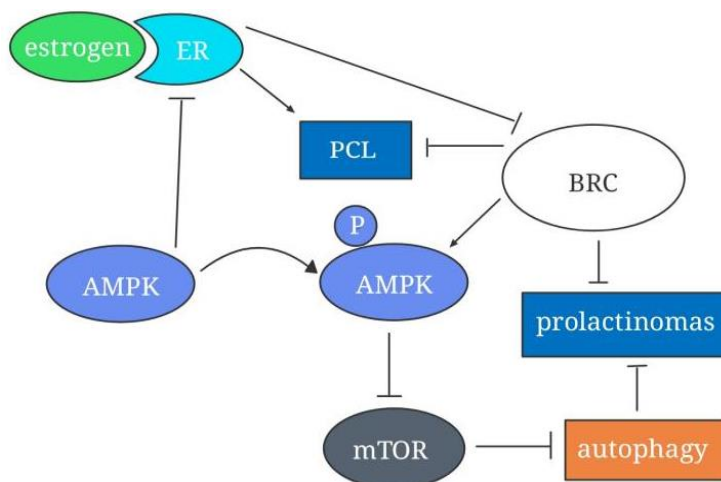
BRC enhances AMP-activated protein kinase (AMPK) phosphorylation and downregulates estrogen receptor (ER) expression in prolactinomas cells.

PRL secretion can be stimulated by estrogen that inhibit the function of DAs [2, 3, 7]. AMPK signal pathway inhibits estrogen secretion and its relevant receptor expression, such as ER $\alpha$  and ER $\beta$ , resulting in the reduction of PRL levels and inhibition of prolactinomas proliferation.

The binding of estrogen and ER can inhibit the effect of DAs that including BRC, and the expression of ER is positively correlated with the level of PRL. ER is also highly and instinctively expressed in aggressive prolactinomas, attenuating the effect of BRC that inferior expression of ER,

and eventually increase drug resistance of BRC in both aggressive and traditional prolactinomas cell [2, 3, 17].

AMPK down-regulates the expression of ER, which makes prolactinomas cells insensitive to estrogen then reduces PRL level [17]. In addition, AMPK phosphorylation can induce autophagy regulatory pathway in prolactinomas cells by inhibiting mTOR pathway [9, 17] (Figure 1).



**Figure 1.** BRC enhances AMPK phosphorylation and downregulates ER expression in prolactinomas cells

### 3. The main drug treatment program

#### 3.1. Increase the dose of BRC

Since BRC is relatively cheap and can be provided by most hospitals, increasing the dose of BRC is feasible to treat patients with BRC resistance from the perspective of economy.

It has been reported that 15 % of patients with prolactinomas showed a decrease in PRL levels that was linked to an increase in the drug's dosage [7]. However, the tolerability of patients and the intensity of side effects should be fully considered, when increasing the dose. This treatment is feasible when patients respond to increasing doses without strong side effects. Regardless of drug resistance, BRC can cause gastrointestinal discomfort and nausea in most patients [7]. Approximately 10-20% of the patients could not tolerate the treatment dose of BRC or insisted on taking it because of the strong adverse reactions during the administration of BRC [5].

In addition, due to individual constitution differences, even resistant patients may not be able to tolerate the dose before it reaches the standard. For such patients, whether resistant or not, it is necessary to change the treatment drug reasonably [7]. In another quarter of patients, although they have able to receive high doses of BRC, their PRL levels were difficult to return to normal, and the tumor volume reduction was not as expected [7]. Since the time is positively correlated with the success rate of treatment, patients who have been treated for more than two years have the highest success rate. If the BRC concentration in the serum reaches this value during the efficacy period but PRL cannot be restored to normal after two years of normal administration, it is recommended to replace appropriate drugs for further treatment [18].

#### 3.2. Cabergoline (CAB) as medication replacement

CAB is a DRD2 selective agonist along with BRC. Due to its advantages such as better treatment success rate (BRC: 70-80%, CAB: 80-90%), better tolerability, lower drug resistance, longer interval dose, it has gradually replaced BRC and become the prior choice for the treatment of prolactinomas in many countries [9, 18]. In addition, it has notable availability for treating patients with BRC resistant and invasive giant prolactinomas (IGPs), such as tumor shrinkage and normalization of PRL [9, 17]. It also normalized PRL levels in approximately 80% of patients who were resistant to BRC

[2, 3, 7]. However, few studies have found that there is a favorable response to BRC in CAB resistant patients.

### **3.2.1. Stronger cytotoxic effect caused by higher affinity to dopamine receptor**

CAB not only can induce apoptosis like BRC, but also induce autophagy through a new signaling pathway. DAs can activate DRD2 to induce apoptosis. Compared with BRC, CAB not only has a stronger binding and selective ability to DRD2 [2, 3, 9], but also can activate DRD5. As a result, it then promotes autophagy by activating DRD5-related signaling pathways, hence, it can still inhibit the growth of prolactinoma cells even there is an absence or insensitivity of DRD2 [8]. This allows CAB to break through one of the mechanisms that contribute to BRC resistance, allowing it to work well in BRC-resistant patients who lack the DRD2.

Activation of DRD5 promotes the production of reactive oxygen species (ROS), ROS acts as the downstream signal molecules of mTOR (mammalian target of rapamycin) signal pathway, to inhibit it and eventually lead to autophagic cell death (ACD). Leng et al. treated pituitary tumor cells with DRD5 agonist SKF83959, and found that this reagent could inhibit the growth of tumor cells, and its efficacy was correlated with the expression level of DRD5 [8]. The high expression of DRD5 protein in most secreting prolactinoma cells creates favorable conditions for the efficacy of CAB [8].

CAB inhibited the proliferation of vascular smooth muscle cells (VSMCs) induced by IGF-1 (insulin-like growth factor 1). IGF1 signal pathway can induce relevant protein synthesis, tumor migration and proliferation of VSMCs that related to carcinogenesis. This function by binding to relevant receptors, such as IGF-1 receptor (IGF-1R). CAB inhibits VSMCs proliferation by activating DRD1 and DRD5 and inhibiting mTOR pathway that related to proliferation of VSMC and ACD, to attenuate IGF1 expression and phosphorylation, then down-regulate IGF-1R expression [8, 13, 17]. BRC activates DRD2 and antagonizes DRD1 at the same time [8, 9], which is one of the possible reasons for the weaker therapeutic effect than that of CAB.

### **3.2.2. Resistance of CAB**

Because the long half-life period, CAB has extended interval dose and mild side effects, hence patients are well-tolerated and less dependent. About 15% of patients are resistant to CAB and 25% are resistant to BRC [7]. At present, CAB resistance is defined as a dose of more than 2mg/wk, but the serum PRL level does not return to normal and the tumor size does not decrease to half of its original [5].

### **3.2.3. Reduce the dose of CAB gradually to reduce side effects and drug dependence**

The study of Paepegaey et al. [19] found that, when the PRL level of patients returned to normal, doctors gradually tended to reduce the dose of CAB to help patients find the minimum dose that can maintain the normal PRL level. The gradual reduction of CAB dose has no negative effect on tumor volume, in addition, this may reduce the adverse effect of CAB. The main reason for the failure of this treatment is CAB resistance, that patient with this feature will have high level of PRL level and larger tumor volume. This is often characteristic of macroadenomas and aggressive prolactinomas. This means that this kind of patients need high doses of CAB to control PRL level and tumor volume. Meanwhile, among DAs, CAB is considered to be the most effective agent for the treatment of high levels of PRL and tumor shrinkage [17, 18]. However, the probability of failure of this treatment is not high (<30%). Moreover, it can also help to identify whether patients with prolactinoma recurrence after CAB discontinuation, to prevent predictably recurrence [19]. In addition, Hu et al. demonstrated that over one-third of patients had sustained remission of PRL levels after discontinuation of CAB. This provides another piece of evidence that this treatment is feasible [20]. It is important to note that this treatment should be continued for at least 2 years, as a short duration of treatment is beneficial for prolactinoma recurrence [18].

### **3.2.4. Risk of taking high doses of CAB**

Reduce the dose of CAB gradually helps avoid serious side effects and reduces the risk associated with long-term use of high-dose of it(>10mg/w) [19]. High doses of CAB related to cardiac

valvulopathy, which is more common in people with Parkinson's disease [17]. However, because the standard dose of CAB used for prolactinomas is much lower than for Parkinson's disease, the risk of induction of cardiac valvulopathy is low even at high doses of it [17]. In addition, high doses of CAB may even lead to increased tumor volume [10]. Anyhow, this treatment reduces the risk associated with long-term use of high-dose CAB [19].

### **3.3. Temozolomide (TMZ) as medication replacement**

A small number of patients are resistant to both BRC and CAB, and neither high dose BRC or CAB treatment can achieve the desired effect. When the prolactinomas of patients are both drug-resistant and aggressive, it is difficult to be treated by BRC, high doses of CAB and standard doses of TMZ are suggested [1].

TMZ is an oral alkylating agent, which is the last conservative treatment for refractory and aggressive tumor, including prolactinomas [7]. TMZ can control about 70% of prolactinomas cell proliferation, normalize PRL level, and have less adverse effect [4, 21]. However, when high O6 methylguanine DNA methyltransferase (MGMT) is highly expressed in prolactinomas cells, patients are resistant to TMZ [7, 22].

#### **3.3.1. Effective for BRC-resistant invasive prolactinoma**

Aggressive prolactinomas are resistant to conventional DAs therapy [21, 22]. Tang et al. found that the expression of DRD2 was low in drug-resistant and aggressive prolactinomas cells, resulting in inferior efficacy of BRC and CAB in the treatment of it. When high dose CAB is used to treat patients with aggressive prolactinoma, the tumor volume even increases, although the probability is low [10]. When conventional treatment fails to achieve the desired efficacy, or even produces serious side effects, TMZ is an effective and popular way that has been proved by experiments, and its efficacy is linearly related to its dose [23]. Over half of patients with prolactinomas have achieved positive therapeutic effects after receiving TMZ treatment [4].

#### **3.3.2. Easy to relapse and have drug resistance**

As a chemotherapy drug, TMZ has rapid efficacy and excellent tolerability for BRC-resistant aggressive prolactinomas, but it is easy to develop drug resistance [6, 21]. High MGMT expression and mutation of MSH6 (mismatch repair protein) can induce resistance to TMZ. Therefore, MGMT can be used as a marker to evaluate the efficacy of TMZ, and MSH6 is positively correlated with the shrinkage of prolactinomas [6, 22, 23] (Table 2).

Capecitabine can attenuate the repair effect of MGMT, reduce the expression of it, then, make prolactinomas cells highly sensitive to TMZ and enhance the therapeutic effect of TMZ [10]. Ishida et al. found that using TMZ and CAPTEM combination therapy was more effective than using TMZ alone. This combination therapy also has certain positive effects in prolactinomas cells with high MGMT expression. Although more data are not available to support the efficacy of CAPTEM, the authors concluded that CAPTEM is more effective than TMZ in patients who are sensitive to TMZ [22].

**Table 2.** Relationship with MGMT expression and dose of TMZ [23]

| Age       | tumor type                             | TMZ dose                                                                                                                 | MGMT expression    | Outcome                                                                            |
|-----------|----------------------------------------|--------------------------------------------------------------------------------------------------------------------------|--------------------|------------------------------------------------------------------------------------|
| 34yrs     | Prolactin-secreting pituitary          | 200 mg/m2 orally for 5 days, 28 day cycle, 6 cycle                                                                       | Immunonegative     | Prolactin drop from 148,751 mU/L to 730mU/L                                        |
| 32yrs     | Prolactin-secreting pituitary          | 200 mg/m2 orally for 5 days, 28 day cycle, 6 cycle                                                                       | Immunonegative     | Prolactin drop from 24,000 mU/L to 4540mU/L                                        |
| 13yrs     | Prolactin-secreting pituitary          | 200 mg/m2 orally for 5 days, 28 day cycle, 12 cycle                                                                      | Immunonegative     | Prolactin drop from 49,000 mU/L to 3515mU/L                                        |
| 13 months | Pituitary blastoma                     | 100 mg/m2 orally for 5 days, 28 day cycle, 12+6 cycle                                                                    | Varied from 40-60% | Temporary regression followed by tumor progression. pituitary hormones normal.     |
| 65yrs     | Pituitary macroadenoma with metastasis | 200 mg/m2 orally for 5 days, 28 day cycle, 15 cycle with 6 weeks break for bilateral adrenalectomy between cycle 7 and 8 | Low                | ACTH drop from 5685 ng/L to 2318 ng/L following break:3519 ng/L to ~pre-op levels. |
| 54yrs     | Prolactin producing macroadenoma       | 200 mg/m2 orally for 5 days, 28 day cycle, 5 cycle and 2 sessions of carboplatin-VP16                                    | N/A                | Failure to control tumor progression. Presence of metastasis.                      |

#### 4. Conclusion

DAs have been shown to be very effective in the treatment of prolactinomas, and their effectiveness depends mainly on DRD2 and ER expression. Low expression of DRD2 will lead to resistance to DAs, contrary to ER. Thereby, there are still some patients who are intolerant or resistant to DAs. BRC is one of the most commonly used DAs with a long history of use. When patients are resistant to it, it is suggested to increase its dose reasonably. However, since BRC itself has certain side effects, such as nausea and vomit, for patients who with intolerance and/or drug resistance with it, may not be possible to bear more serious side effects brought by the high dose, hence, it is recommended to replace other drugs that belong to DAs.

CAB is another DAs that is most widely used. Although its side effects are similar to those of BRC, it is more acceptable for patients because of its better efficacy, less degree of side effects, and longer drug interval. In addition to mediating DRD2-related signaling pathways, CAB can also activate DRD1-related signal pathways antagonized by BRC that resistant to DRD1. Although the percentage of patients with resistant is lower than that of BRC, recent research has found that high-dose CAB has a low risk of leading to tumor progression. In addition, for patients with Parkinson's disease, long-term use of high-dose CAB has a risk of inducing cardiac valvulopathy. Therefore, TMZ treatment is recommended for patients with complete CAB resistance.

TMZ is a last-resort treatment for aggressive tumors when high-dose DAs have failed. Although studies have proved that patients treated with TMZ for a long time have a high overall survival rate and can avoid a high failure rate in the second TMZ treatment after tumor regeneration, TMZ is more prone to drug resistance than other drugs, and tumors treated with this method are prone to relapse, and even 20% of patients show tumor progression. Despite Capecitabine combined with TMZ treatment can increase the sensitivity of prolactinomas to TMZ, there are still insufficient data to prove the effectiveness of this method.

Studies have found that DRD5 can effectively inhibit the growth of pituitary tumors. DRD5 protein is highly expressed in human and is involved in CAB mediated tumor growth inhibition, and inhibits VSMC proliferation. Therefore, DAs targeting the DRD5 may be a new treatment for prolactinomas.

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