# Effectivity of Bromocriptine Administration Towards Prolactin Positive Breast Cancer Receiving Anthracycline-Based Chemotherapy: A Literature Review

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## ABSTRACT

*Breast cancer is among the deadliest gynecology cancers in the world. However, the management of advanced-stage breast cancer is often harder as a result of chemoresistance. This review aimed to discover the effect of bromocriptine on prolactin-positive breast cancer patients who received anthracycline-based chemotherapy. It is known that anthracycline works by inhibiting topoisomerase IIα (TOP2A), forming free radicals, binding DNA, and altering cell homeostasis, hence stopping the cell cycle and inducing cell death. However, reduction of TOP2A expression and increased glutathione s-transferase (GST) and ATP-binding cassette (ATP) membrane activity increase anthracycline efflux from the cell membrane, hence reducing its effectivity. Prolactin is one of the most common chemoresistance agents whose complex with its receptor will induce JAK/STAT pathway to increase GST. The regulation of Bcl-2 and ERK was also determined by prolactin. Bromocriptine is an agonist of the D2 dopamine receptor that inhibits adenyl cyclase and a D1 dopamine weak antagonist. Bromocriptine could reduce prolactin serum and receptors in various cases. Some studies have found that bromocriptine could improve the effectiveness of chemotherapy regimens, including cancer-related hyperprolactinemia, breast cancer that underwent cisplatin, and taxanes. Therefore, bromocriptine offers potential as it could improve outcomes and reduce resistance in prolactin-positive breast cancer patients who are administered anthracycline-based neoadjuvant chemotherapy.*

***Keywords:*** *breast cancer, bromocriptine, chemotherapy, prolactin, receptor.*

## INTRODUCTION

Breast cancer is the most common gynecological malignancy in the world. Data from the International Agency for Research Cancer reported that the incidence of breast cancer was as high as 11.6% in 2018. Breast cancer contributes to the most death by cancer, above lung and colorectal cancer.[1,2] About 60 to 70 per cent of breast cancer patients are diagnosed in late stages (III or IV).[3] Breast cancer treatment involves various modalities, including neoadjuvant chemotherapy. Neoadjuvant chemotherapy is aimed at making tumors likelier to be resected, hence improving the chance of breast-conserving operations in some cases.[4] Neoadjuvant chemotherapy is also beneficial in eradicating micrometastasis and reducing surgical morbidity in patients with axillary node involvement.[4–6]

There are various chemotherapy regiments for tumor eradication, including anthracycline, which consists of doxorubicin, epirubicin, idarubicin, and daunorubicin. Anthracycline can cause irreversible defects in cancer cells

by inhibiting the topoisomerase IIα (TOP2A) enzyme in the cell nucleus. This process could stop the DNA replication process and started apoptosis.[7,8] There is some evidence of anthracycline-based chemotherapy. Nakajima reported that breast cancer stage II to III patients showed a positive response toward anthracycline-based chemotherapy, with an overall survival rate of 83.4%.[9] Another study suggested that response rates in triple-negative, HER2-positive, luminal B, and luminal A were 87.5%, 80%, 61.2%, and 55.2%, respectively.[10]

Chemoresistance is one of the biggest burdens of cancer therapy. Chemoresistance was found in various chemotherapy regimens, including anthracycline. Chemoresistance toward anthracycline is developed through reduction of TOP2A expression, elevation of GST, and elevation of ATP binding cassette (ABS) membrane transporter's expression.[11,12] Another neglected chemoresistance mechanism is complex between prolactin and prolactin receptor.[13] Prolactin physiologically helps secretion, differentiation, stimulation, and proliferation of breast cells. On the other hand, prolactin was linked to aggressivity of tumour.[13–15] A study in Indonesia found that 62.5% of advanced stage breast cancer patients showed prolactin receptor expression.[16] Another study found that more than 90 per cent of pre-menopausal women with breast cancer expressed prolactin receptor.[17]

Bromocriptine is an alkaloid ergot with high selectivity toward the D2 dopamine receptor, which could reduce prolactin secretion in the anterior hypophysis.[18,19] A study reported that low-dose bromocriptine (2.5 mg) could normalize prolactin levels in breast cancer and prostate cancer patients for 24 hours. The same dose is also considered beneficial as supplementary drug to endocrine therapy or chemotherapy.[20] Another study suggested that there was synergy between bromocriptine and doxorubicin or paclixatel in inhibiting the growth of leukemic cell CEM/ADR5000.[21] Therefore, we conducted a literature review to review chemoresistance in prolactin-positive breast cancer receiving anthracycline-based chemotherapy and bromocriptine administration effectivity in the population.

## BASIC KNOWLEDGE OF BREAST CANCER

Breast cancer is one of the most common types of women's cancers in the world. Data from Global Cancer Statistics (Globocan) stated that there were 2,088,849 incidences of breast cancer in 2018.[1] About 43.6% of these were found in Asia. The data also estimated that 1 out of 4 women who was diagnosed with cancer was diagnosed with breast cancer. Breast cancer was ranked as the fifth most fatal cancer and the most fatal woman cancer.[1,2] Breast cancer could be caused by various factors, which are categorized into demographic, reproductive, hormonal, hereditary, lifestyle, and other factors. These factors are grouped as intrinsic and extrinsic based on their nature of origin. Intrinsic factors included age, gender, race, and genetic predisposition. These intrinsic factors are independent parameters that cannot be modified. Extrinsic factors are modifiable and are commonly targeted in breast cancer prevention strategies.[22,23]

Based on molecular subtype, breast cancer is divided into luminal A, luminal B, HER2+, and triple-negative/basal-like which is categorized based on estrogen receptor, progesterone receptor, and HER2 expression on immunohistochemistry examination.[24] A study in Indonesia showed that luminal B was the most common subtype found (43.9%), followed by HER2-positive (14.6%), luminal A (14.0%), and basal-like (11.3%). The same study also found a significant relationship between tumor stage and TOP2A expression with molecular subtypes.[25] Another study conducted in Indonesia showed that luminal A was the most common type found, followed with triple-negative/basal-like, HER2-positive, and luminal B, with proportions of 38.1%, 25.0%, 20.2%, and 16.7%, respectively. The study stated significant differences in age, histological gradation, stage, and lymph nodes' status between subtypes.[26] A nationwide study in Indonesia showed that luminal A was the most common type found, followed by triple-negative, HER2-positive, and luminal B. Luminal B was the most common type found in the age group below 40 years old. HER2-positive was the most common type found

in the age group older than 50 years. Larger tumor size was observed in triple-negative/basal-like tumour.[27]

## ANTHRACYCLINE-BASED NEOADJUVANT THERAPY

Anthracycline is one of the agents used for neoadjuvant chemotherapy, which aims to change an inoperable state into an operable state and to downgrade mastectomy to a more conservative surgical option.[28] It is extracted from *Streptomyces peucetius* var. *caesius*. Anthracycline covers large therapy options, including doxorubicin, epirubicin, idarubicin, and daunorubicin, which differ in chemical structure and cell activity. Doxorubicin and epirubicin are used for solid tumors, whereas daunorubicin and idarubicin are mainly used for acute leukemia. Anthracycline is given through circulation and extensively metabolized in the liver, 50% of which is excreted through biliary excretion. An anthracycline therapeutic effect is reached after being converted into intermediate alcohol form. Anthracycline is distributed rapidly into various organs but cannot pass the blood-brain barrier.[7,8]

Anthracycline works through four main processes. Anthracycline inhibits TOP2A, forms free radicals, which are semiquinone and iron-dependent reactive oxidative species (ROS), binds DNA through an intercalation process that blocks DNA and RNA synthesis, and impairs ion transport and fluid metabolism through its binding toward the cell membrane.[8,29] Anthracycline active metabolites passively diffuse into the cell and bind proteosomes. Anthracycline is then translocated from the cell nucleus cytoplasm through the help of ATP, further binding with DNA. Anthracycline works by blocking catalytic enzymes, which stabilize DNA chain separation in a covalent way. Anthracycline causes irreversible DNA damage, which is mediated by TOP2A in actively proliferating cancer cells. Anthracycline also works by inhibiting the TOP2A enzyme in the cell nucleus and inhibiting double-bond DNA formation; hence, DNA replication stops, and apoptosis is induced as a result of the inability to repair or replicate DNA. Anthracycline also works as a DNA intercalator that could insert a planar ring within the DNA base, thus preventing replication and transcription of DNA.[29] In addition, binding between anthracycline and the cell membrane could impair fluid balance and ion transport. This phenomenon could induce the production of free radicals within cells. The quinone component of anthracycline reacts with oxygen and produces radical anion superoxide. This causes peroxidase and superoxide production, which could impair DNA and cause DNA base oxidation, leading to apoptosis. The formation of these free radicals is significantly mediated by the interaction of anthracycline and the iron component.[8]

Anthracycline-based chemotherapy has been proven effective in various studies. A study showed that good responses were found in luminal A, luminal B, HER2, and triple-negative breast cancers that received anthracycline-based chemotherapy with response rates of 55.2%, 61.2%, 80.0%, and 87.5%, respectively.[10] Another study showed that anthracycline was effective in breast cancers with negative estrogen receptors, a high S-phase fraction ratio, and a high Ki-67 level.[30] It was reported that TOP2A was one predictive effect of the factor. However, a recent study did not find a correlation between TOP2A expression and breast cancer response or survival. The study also found that a positive response to breast cancer was independently associated with TOP2A expression.[31]

## CHEMORESISTANCE TOWARD ANTHRACYCLINE-BASED NEOADJUVANT CHEMOTHERAPY

Chemoresistance toward anthracycline-based regiments results from various mechanisms, including reduction of TOP2A expression, increase of Glutathione S-transferase activity, or increase of ABC membrane transporter expression, all of which could reduce chemotherapy toxicity.[32] Topoisomerase II alpha (TOP2A) enzyme is the main target of anthracycline-based chemotherapy. Therefore, downregulation of TOP2A is suspected to cause resistance in anthracycline-based regiment.[33] Suppression of TOP2A could induce chemoresistance toward doxorubicin. A study suggested that cells that express TOP2A at a low

level tend to be more resistant to chemotherapy regimens. This was explained by the reduction of the TOP2-DNA complex, which could cause less tumor cell DNA that experiences impairment due to anthracycline administration. Therefore, it was reported that patients with TOP2A deletion were less responsive to doxorubicin administration.[31,33]

Another mechanism that could explain chemoresistance is inactivation by glutathione S-transferase (GST), which is a phase II detoxification enzyme whose function is to protect macromolecules by forming electrophilic components. GST catalyzes glutathione conjugation toward the chemotherapy regiment's metabolite, which could fasten the effective duration of medication within cells, hence reducing the effectivity of the chemotherapy regiment.[34,35] ABC component also accounted for anthracycline-based chemotherapy chemoresistance. ABC is found to cause medicine metabolite efflux through MDRP1, which codes P-gp. A study mentioned that anthracycline uptake was found to be reduced substantially alongside an increase in ABS transporter expression (ABCb1, ABCc1, ABCc2).[36,37]

The expression of the superfamily aldo-keto reductase (AKRs) enzyme is another factor in chemoresistance to this regimen. AKRs change ketones and aldehydes into primary and secondary alcohols. AKR expression is regulated by osmotic pressure, AP-1 transcription factor, and anthracycline-generated reactive oxygen species (ROS).[38,39] AKR1C metabolizes various chemotherapy agents, including doxorubicin. AKR1A1 and AKR1C2 could converse the anti-tumor agent doxorubicin into doxorubicinol, which is less toxic. Another substance called carbonyl reductase and quinone oxidoreductase-1 (NQO1) could metabolize doxorubicin into doxorubicinol. This conversion could cause a change of medicine localization into lysosome, which impairs the ability to penetrate the cell nucleus.[38]

One of the effects of anthracycline administration is increasing free radicals and reactive oxidative species through an enzyme-mediated process as a result of anthracycline toxicity. This phenomenon induces a protective mechanism to reduce free radicals, called a glutathione-dependent protective mechanism, which is also related to doxorubicin chemoresistance.[40,41] Change of p53

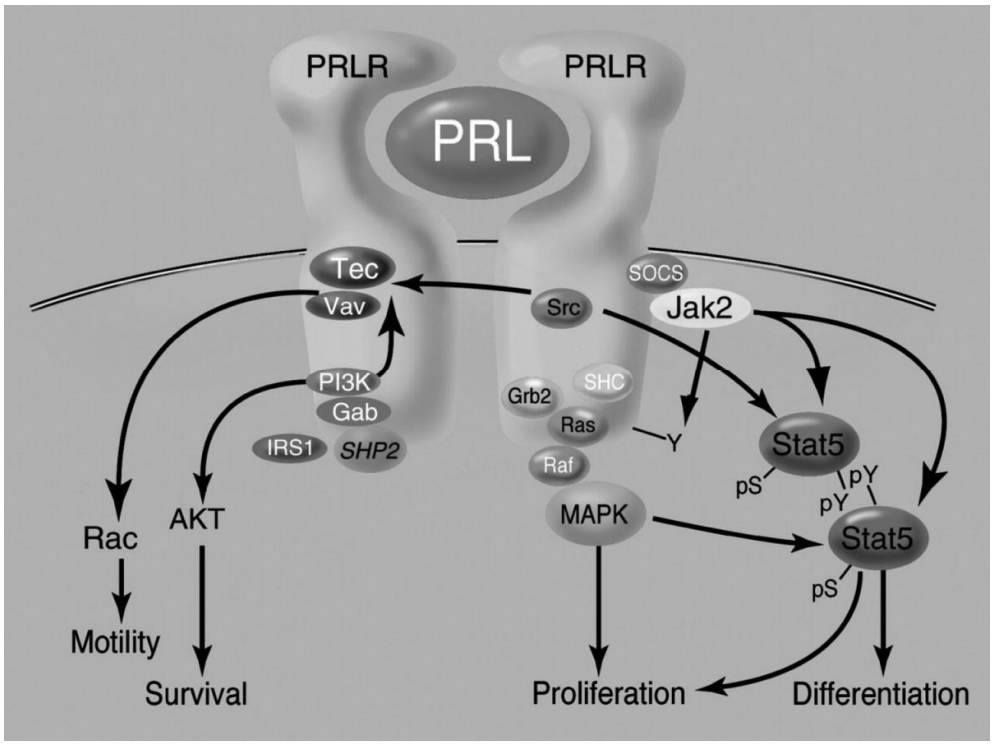


**Figure 1.** Complex of ligand PRL-RP, JAK/STAT, and MAP kinase.[46]

is also related to doxorubicin administration, which could reduce the apoptosis effect of chemotherapy. Another study suggested a positive relationship between transmembrane TNF-α and anthracycline resistance. It was found that transmembrane TNF-α was present in more than 50% of patients' breasts, which could impair breast cancer cells' sensitivity toward doxorubicin.[42]

## PROLACTIN ROLE IN BREAST CANCER AND CHEMORESISTANCE

Prolactin is a 23-kDa-sized hormone that is mainly produced by the hypophysis, with the breast as its main target. Prolactin is categorized as a lactogen protein that consists of a homologous structure.[43,44] Prolactin could promote malignant cells' proliferation and differentiation (**Figure 1**). This was proven by various studies that linked high prolactin levels with tumor cell progression, both in vitro and in vivo.[45] Prolactin was also linked with the failure of chemotherapy and management. Prolactin binds with the prolactin receptor to induce the signaling cascade and the Janus kinase-signal transducer and activator of transcription (JAK-STAT) cascade. Prolactin also induces other cascades, such as Ras-Raf-MAPK, ERK1/2, and c-Jun N-terminal kinase.[13]

The prolactin receptor is a cytokine receptor that serves as a single-pass membrane. The prolactin receptor isoform weighs 80 kDa. The prolactin receptor is mainly mediated through JAK2/STAT5 pathway, but also through other signaling pathways.[47] Prolactin receptor activation needs ligand binding in two places where one place should have higher affinity. This bond activates the ternary complex, which consists of one molecule hormone and a homodimer receptor.[48] This receptor could also bind to placental lactogens and growth hormones. Unlike estrogen, which could bind to classic and non-classic receptors, prolactin only has one specific receptor).[45,49]However, prolactin could form various isoforms that could be processed by various signaling cascades.[49] There is a relationship between prolactin receptors and classic estrogen receptors on various levels.[50]

Increased expression of prolactin receptors and prolactin levels are associated with the risk of tumor progression, invasion, and metastasis.[51] Various studies have reported the majority of breast cancers on human-expressed prolactin. Prolactin receptor expression is found positive in 80 to 90 per cent of breast cancer.[13] A prospective study demonstrated that prolactin and prolactin receptors were found in up to 95% and 60% of breast cancer cases in women and men, respectively.[52,53] A large-scale study in Poland showed that almost 83% of breast cancer cases on 142 pre-menopausal women and 594 post-menopausal women showed prolactin receptor expression.[54] A study in Indonesia showed that 62.5% receptor samples showed prolactin receptor expression.[16]

Prolactin is an important component of breast cancer chemoresistance, but it is often neglected. An epidemiology study mentioned that chemoresistance and lower survival rates were related to higher prolactin levels. It was also mentioned that the prolactin and prolactin receptor complex improved the expression and activity of GST, which was mainly mediated through JAK/STAT.[13] Besides JAK/STAT, this complex was mediated by MAPK. A study found that there was an antagonist effect of prolactin toward cisplatin-induced apoptosis.[55] Binding between prolactin and its receptor induces JAK/STAT and Ras-Raf-MAPK pathway activation. These phenomena activate GST, which conjugates cisplatin into glutathione.[13] Glutathione activation increases efflux and minimalizes DNA impairments. GST activates regiments that are based on platinum, doxorubicin, cyclophosphamide, and etoposide, but not in microtubule-based regiment.[55,56] Chemoresistance mechanism which was not linked with GST, could involve alterations of Bcl-2 protein (**Figure 2**).[13]

Other than JAK/STAT pathway, prolactin could synergize with IGF-I and EGF-family ligand to activate MAPKs and AKT. This pathway contributes to gene expression, which is related to proliferation, survival, and invasiveness. Furthermore, this activation is linked to chemoresistance toward endocrine therapy, molecular therapy, chemotherapy, and radiotherapy.[13] ERK1/2 (MAPK) and

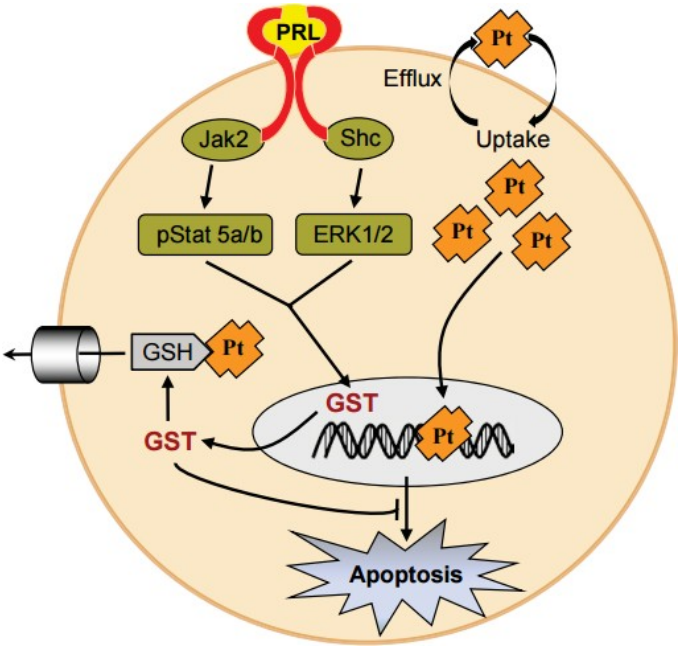


**Figure 2.** Mechanism of cisplatin chemoresistance by prolactin.[56]

AKT activation could also induce estrogen and prolactin receptors, which could increase transcription and degradation activity. The prolactin pathway through JAK2/STAT5 will increase estrogen receptor expression, which could increase estrogen sensitivity and estrogen-targeted gene expression, including the prolactin receptor.[57] A study found that there was a prolactin and hormone/cytokine role in activating the STAT5 pathway and intervening in cell cycle function, which was regulated by BRCA1 wild type.[58]

Endogenous prolactin's ability to reduce chemotherapy regiment efficacy was also observed in an in vitro study that used ceramide metabolites to mediate apoptosis induction as a result of stress stimulation and receptor death through gamma irradiation. It was observed that breast cancer cells that produced prolactin were more resistant to ceramide-induced apoptosis than non-prolactin-producing cells.[59]

## BROMOCRIPTINE ADMINISTRATION TOWARD BREAST CANCER

Bromocriptine is a dopamine agonist that can inhibit prolactin release, which is triggered by the prolactin-releasing hormone (PRH). Bromocriptine specifically works as an agonist in the D2 dopamine receptor and inhibits adenylyl cyclase. Bromocriptine is a weak antagonist of the D1 dopamine receptor and an alkaloid ergot, which is extracted from the *Claviceps purpurea* fungus. This fungus produces histamine, acetylcholine, tyramine, and other active biological substances. Bromocriptine has various effects on receptors, including the adrenoreceptor, serotonin receptor, 5-HT receptor, and dopamine receptor. Bromocriptine and other ergot derivates have high selectivity toward hypophyseal dopamine receptors, thus directly suppressing prolactin secretion from hypophyseal cells through the regulation of dopamine receptor.[19,20]

Bromocriptine has been used on various occasions. Mostly, bromocriptine is used for parkinsonism therapy through the inhibition of dopamine receptors in the nigrostriatal tract. Bromocriptine is also used for hyperprolactinemia and acromegaly through inhibition of the tuberoinfundibular tract.[60] Other newer studies suggested that bromocriptine was useful against diabetes mellitus and other diseases.[19,20,61] Bromocriptine was also found to be useful against hypophyseal tumors and other tumours.[19,20]

Bromocriptine is usually administered orally, which has good absorption. However,

bromocriptine is extensively extracted and metabolized in the liver; hence, only 7% of absorbed materials can reach systemic circulation with a half-life of 2–8 hours.[20] Bromocriptine has already been available in a slow-release dose, which could reduce the frequency of medicine consumption. Other than oral, bromocriptine could be administered through the intravaginal method, which provides fewer gastrointestinal adverse effects.[19,20] Bromocriptine is metabolized extensively in the liver through the help of cytochrome P450 oxygenase before returning to circulation. Therefore, medications that interfere with the same metabolic pathway could reduce bromocriptine degradation; hence, dose adjustment is needed.[62]

Bromocriptine is commonly consumed twice to thrice daily at a 2.5 mg dose. The same dose is used to suppress physiological lactation in some conditions, even though it was reported to be linked with postpartum cardiotoxicity.[20] In order to avoid toxicity, research suggested that bromocriptine should be given from 1,25 mg low dose at night, then increased to twice a day 2.5 mg dose or once a day 5 mg dose after one week or according to patient's tolerance.[19] A study showed that bromocriptine administration significantly reduced breast milk production after 7 days of giving birth.[62]

Bromocriptine is a Food and Drug Administration (FDA)-approved medication, as it is considered safe to use for parkinsonism. Today, bromocriptine usage is being developed, which is being studied in relation to diabetes. Bromocriptine repurposing is also being developed toward cancer therapy.[21] Recent study showed that low dose bromocriptine administration could normalize prolactin levels on cancer-related hyperprolactinemia through a 24-hour period. This dose was considered beneficial for endocrine therapy or chemotherapy, including in metastatic breast cancer thrapy.[20]

A recent study showed that there was an increase in high-dose cisplatin cytotoxic effects toward T47D cells that were given additional therapy with the hPRL G129 antagonist. This showed that endogenous prolactin protected tumor cells from chemotherapy regiment's cytotoxic effects.[63] Another study suggested that there was improvement in cancer response when bromocriptine was added to the therapy regiment.[64] An in vitro study found that combination of bromocriptine and doxorubicin/paclitaxel gave synergistic inhibition effects toward CEM/ADR5000 leukemia cells' growth which was measured using resazurin assay.[21] These findings reciprocated other findings which reported that bromocriptine showed cytotoxic effect on a broad range of cancer cells, including those that were multi-resistance toward common treatment and expressing P-glycoprotein. A previous study also found that bromocriptine administration of 1.25–2.50 mg/day for 5 days showed a significant decrease in prolactin levels and tumor cells in the synthesis phase of the cell cycle.[21,65]

Previous studies have not successfully determined the benefits of bromocriptine in lowering prolactin levels in breast cancer patients receiving tamoxifen. This failure was explained by the fact that hypophyseal and extra-hypophyseal prolactin expression were regulated by different regulators under various lactogen effectors. Therefore, inhibition of the prolactin receptor is not guaranteed to be beneficial in breast cancer therapy. These facts support the idea that prolactin receptor inhibition and suppression are considered more beneficial and effective in increasing the response to chemotherapy by administering bromocriptine, although there is still yet to be done.[66]

## CONCLUSION

Neoadjuvant chemotherapy is required in advanced-stage breast cancer to increase operability, quality of life, and survival. Anthracycline is a potential chemotherapy agent. However, chemoresistance is a challenging factor in chemotherapy, which is commonly caused by prolactin and prolactin receptor expression. Amid chemotherapy resistance, bromocriptine offers potential, as bromocriptine could improve outcomes and reduce resistance in prolactin-positive breast cancer patients who are administered anthracycline-based neoadjuvant chemotherapy.

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