

## Propranolol in Chemotherapy Induced Alopecia Review

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### Original Research Article

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**Abstract:** Alopecia actuated by chemotherapy is a much-feared unfavorable impact by numerous chemotherapy protocols. Alopecia induced by chemotherapy is considered the most mental stunning highlights of cancer treatment. A few medicines have been researched as conceivable approaches to anticipate hair loss, however, none has been effective. To date, still no accomplishable approach or treatment for overcoming chemotherapy-induced alopecia. Utilizing developed new sub-atomic innovation, spots and featuring in understanding sub-atomic systems of chemotherapy-prompted alopecia has been accomplished utilizing rat models. Numerous systems can clarify the pathobiology of the response of human hair follicle to chemotherapy albeit some to a great extent stays obscure. In this article, we audit pathobiology of chemotherapy-initiated alopecia, we concentrate on the roles of p53, CDK2 and its objective qualities that are vital in interceding reactions of hair follicle cells. We expect that nearby pharmacological hindrance of p53 and CDK2 activity may fill in as an effective treatment to avert chemotherapy-incited balding. Adequate pharmacological inhibition of chemotherapy-induced male pattern baldness may require a blend of inhibitors to block correlative or excess pathways of apoptosis in hair follicles. Estimation chemotherapy instigated alopecia is vital and the related subject we open to it in this review. Moreover, in this review, we will clarify the biomolecular link between the degeneration of hair follicle induced by chemotherapy and the mechanism of propranolol in controlling P53 and CDK2 as protection from alopecia induce by chemotherapy.

**Keywords:** P53, CDK2, propranolol, chemotherapy, alopecia.

## INTRODUCTION

Chemotherapy-induced alopecia (CIA) is thought to be a standout amongst the awful factors in cancer persistent care. CIA can contrarily affect the singular impression of appearance, body picture, sexuality, and confidence, and in addition deny patients of their security, on the grounds that this treatment-related result is promptly connected with having tumor by the lay open. Forty-seven percent of female malignancy patients view CIA as the most awful aspect of chemotherapy and 8% would even decrease treatment inspired by a paranoid fear of this looming side-impact [1-3].

Chemotherapy drugs are potent medications that attack all speedily growing cancer cells. Unluckily, these drugs can not differentiate between default cells and health rapidly dividing cells so chemotherapeutic medications attack the other speedily growing cells all over the body together with those in the hair roots. Chemotherapeutic agents may cause alopecia all over the body not objective on the scalp. The eyebrow, eyelash, pubic, armpit, and other body hair are not excluded also drops out. Chemotherapeutic agents differ from each other to cause CIA, what's more, CIA depends on the chemotherapeutic agent

used, as well as the dose, frequency, duration and route of administration [4].

Fortunately, more often than not balding from chemotherapy is impermanent. The patient can expect to regrow the hair three to six months after ending of chemotherapy, however, the hair may temporarily be an alternate shade or texture. Hair, for the most part, starts dropping out two to a month after beginning of the treatment. It could drop out very rapidly in bunches or step by step. The male pattern baldness will proceed all through the treatment and up to fourteen days subsequently. Regardless of whether the hair diminishes or it turns out to be totally bare will depend on the treatment [4].

No treatment exists that can ensure the hair will not drop out amid or after chemotherapy. The ideal path for the patient to manage approaching balding is to prepare and concentrate on making the persistent alright with the appearance some time recently, amid and after the malignancy treatment [5].

### Incidence of Chemotherapy-Induced alopecia

The estimation of the overall incidence of chemotherapy-induced alopecia is 65%[1]. The

chemotherapeutic agent and chemotherapy protocol affect the prevalence and the severity of CIA [4].

Not all chemotherapy causes alopecia. The following drugs are causing alopecia or thinning: altretamine, cisplatin, cyclophosphamide, docetaxel, doxorubicin, epirubicin, fluorouracil, gemcitabine, idarubicin, ifosfamide, paclitaxel, vincristine and vinorelbine [1, 4, 6].

Numerous classes of chemotherapy can prompt alopecia, through occurrences of CIA divergent through the four main drug classes: for antimicrotubule agents (e.g., paclitaxel) >80%, for topoisomerase inhibitors (e.g., doxorubicin) 60%-100%, for alkylators (e.g., cyclophosphamide) >60%, and for antimetabolites (e.g., 5-fluorouracil plus leucovorin) 10%-50%.

Reasonably combination chemotherapy that consists of two or more chemotherapeutic chemotherapy will produce higher incidences of severe alopecia comparing with monotherapy chemotherapy [1].

#### **Pathobiology of chemotherapy-induced alopecia**

The hair follicle is a lively structure found in mammalian skin. The process of hair growth occurs in distinctive consecutive phases. The first phase is called anagen and is the active growth phase, catagen is the resting phase, telogen is the decline of the hair follicle phase, exogen is the active flaking of hair phase and finally kenogen is the phase between the empty hair follicle and the growth of new hair [7].

Anagen effluvium is the pathologic damage of anagen or growth-phase hairs. Characteristically, it is caused by radiation therapy to the skull and chemotherapy, particularly with alkylating agents [7, 8].

Chemotherapy-induced alopecia is a result of direct toxic effect on the rapidly dividing cells of the hair follicle (anagen phase). While hair loss from chemotherapy has been characterized as acute diffuse flaking that is produced by dystrophic anagen effluvium, [8] actually, chemotherapy-induced alopecia may present with diverse pathomechanisms and clinical forms. Corroboration happens representing that the hair follicle may respond to the same dreadful effect of chemotherapy that is able of stopping mitosis with both cracking patterns, i.e., dystrophic anagen effluvium and telogen effluvium [9]. Consequently, the hair may drop out very quickly in clusters or slowly. Once the mitotic activity is ceased, various and interrelating factors may effect the flaking pattern. The main factor is the mitotic activity of the hair follicle at the moment of the insult [10].

The anagen hair follicle the epithelial part goes through the active proliferation, with the bulb matrix cells revealing the extreme proliferative action in

building up the hair trough. The sudden termination of mitotic activity leads to fading of the incompletely keratinized to the hair, resulting in contraction and succeeding cracking inside the hair canal. The significance is hair flaking that frequently commences at 1 to 3 weeks after launch of chemotherapy. Owing to its extended anagen phase, the scalp is the most communal location for hair loss, generally, the scalp hair around 90% are in the anagen stage, and as such, hair loss is usually plentiful and results in alopecia that is unfortunately fairly apparent.

Once hair become in the late anagen stage, the mitotic rate will slightly slows down naturally, it basically hastens its normal pathway to telogen phase, however mitotically inactive phases (catagen and telogen) are not affected by chemotherapy [11].

In general, chemotherapy-induced alopecia is reversible, hair regrowth naturally arising after a delay of 3 to 6 months. The new hair growth appearances show changes in color and/or texture in some patients. Hairs may be curlier than previous hair before chemotherapy or they may be gray until the follicular melanocytes begin functioning again, but these differences are usually temporary. Chemotherapy with busulfan and cyclophosphamide following bone marrow transplantation could cause permanent alopecia [12]. Permanent alopecia has also been associated with certain risk factors that may be chronic graft-versus-host reaction, previous exposure to X-ray, and age of patients [13].

Developments made in considerate the pathobiology of chemotherapy-induced hair loss, in combination with the exploration of several experimental pharmacologic methods, may offer some optimism. However, the inherent vulnerability rests with the rapid cell proliferation of hair follicle keratinocytes during anagen that renders the structure susceptible to the effects of chemotherapeutic toxicity. A strategy that protects against chemotherapy-induced hair loss may involve arresting the cell cycle in order to reduce the sensitivity of the follicular epithelium to cell cycle-active antitumor agents. Inhibition of cyclin-dependent kinase 2 (CDK2), a positive regulator of the eukaryotic cell cycle, may represent a potential approach that arrests the cell cycle. Potent small-molecule inhibitors of CDK2 are currently being developed using structure-based methods [4]. Ultimately, a successful therapeutic candidate should selectively target the hair follicle and avoid interfering with the efficacy of anticancer treatment. In view of the fact that cancer is usually treated with a combination of chemotherapy drugs, an effective mitigation strategy would likely require agents that are effective for different chemotherapeutics with distinct mechanisms of action. Moreover, variations in patient characteristics must also be taken into account, as the pattern of chemotherapy-induced hair loss is patient-

specific [4]. Ultimately, a successful therapeutic candidate should selectively target the hair follicle and avoid interfering with the efficacy of anticancer treatment. In view of the fact that cancer is usually treated with a combination of chemotherapy drugs, an effective mitigation strategy would likely require agents that are effective for different chemotherapeutics with distinct mechanisms of action. Moreover, variations in patient characteristics must also be taken into account, as the pattern of chemotherapy-induced hair loss is patient-specific [14].

P53 another mechanism related to alopecia induced by chemotherapy, P53-dependent apoptosis of hair-matrix keratinocytes and chemotherapy-induced hair-cycle abnormalities, driven by the dystrophic anagen or dystrophic catagen pathway, play important parts in the degree of hair-follicle damage, alopecia phenotype, and hair-regrowth pattern. Additionally, the degree of hair-follicle stem-cell damage determines whether chemotherapy-induced alopecia is reversible [15].

The mechanisms underlying permanent chemotherapy-induced alopecia are unknown, but at present evidence suggest that resistance of epithelial hair-follicle stem cells to apoptosis depends on various factors. Most hair-follicle stem cells are in the G0/G1 phase of the cell cycle and, therefore, are resistant to cell-cycle-specific chemotherapy agents [16, 17]. Enhanced DNA repair via the non-homologous end-joining pathway, which is mediated by PRKDC, and asynchronous DNA synthesis protect the cells from DNA errors induced by replication and repair [18]. During asynchronous DNA synthesis, the parental, immortal, DNA strand always segregates with the stem cell and not the differentiating progeny [18]. This mechanism reduces the risk of being affected by DNA-damaging agents and accumulation of replication-associated mutations. Rapid inhibition of P53 (Cycle-regulating genes) activity in hair-follicle stem cells via increased MDM2 expression promotes survival of hair-follicle stem cells after DNA damage [18]. A P53 null mutation in mice was associated with prevention of cyclophosphamide-induced apoptosis [15]. Stem cells more highly express members of the BCL2 family and other inhibitors of apoptosis than do their differentiated progeny, which also protects the stem-cell compartment [18]. Multidrug-resistant proteins employ ATP hydrolysis to actively efflux drugs from cells, which protects them from cytotoxic effects [19]. In mice, epithelial progenitor cells in skin express high levels of transporter proteins, such as Abcg2 (also known as Bcrp), and P-glycoprotein [19]. Whether homologous efflux transport proteins have similar effects in the human hair-follicle bulge remains to be investigated. Finally, epithelial stem cells in human hair follicles actively obstruct gap junctional transport (eg, downregulation of GJA1 (also known as connexin-43)

expression) [20, 21], which hampers the entry of xenobiotics and small-molecule toxins.

#### **Measurement CIA (chemotherapy induced alopecia)**

In order to evaluate the efficacy of prophylaxis for the prevention of chemotherapy-induced alopecia (CIA), it is essential to precisely quantify the amount of hair mass that is present hair mass index (HMI) wanted to be determined, it will be obtained by cross-section trichometry (CST) that is a suitable parameter for hair mass measurement. Patients receiving chemotherapy were sequentially measured using CST during their treatment. Other tools can be used are World Health Organization (WHO) grade, visual analog scale (VAS) score, and patients' need to wear wig or head cover. T [22]. CST for HMI measurement is a useful mechanical modality for assessing hair loss in CIA patients. It is quantitatively more precise than existing non-mechanical measuring methods. It is recommended when detection of minor changes in hair quantity is required. Marking a fixed sampling area to ensure return to the exact same site is only required when a minor change in pre- and posttreatment HMI values [22-25].

#### **Short introduction in cross-section trichometry**

Using the commercially available version of the cross-section trichometer prototype, HairCheck, hair mass quantity was measured. HairCheck is a hand-held instrument that measures the cross-sectional ratio of an isolated bundle of hair in a premeasured area (2 cm×2 cm) of the scalp and generates a displayed value on a led screen. HMI is the square millimeter of hair per 1 cm<sup>2</sup> of scalp ×100. The sampled hair must be at least 2.5 cm in length at time of testing [22-26]. The Hair-Check system also includes a midline locating device ensuring return to a former sampling site. The HMI measurements were performed between 2.5 and 3.5 cm hair length by the two first authors trained to use the HairCheck system, in accordance with the HairCheck instructions.

#### **Treatment of alopecia induced by chemotherapy**

Several treatments have been investigated as possible ways to prevent hair loss, but none has been absolutely effective, including scalp hypothermia (cryotherapy). During the chemotherapy infusions, ice packs or similar devices are placed on the head to slow blood flow to the scalp. This way, chemotherapy drugs are less likely to have an effect on the hair. Studies of scalp hypothermia have found it works somewhat in the majority of people who have tried it. However, the procedure also causes a small risk of cancer recurring in the scalp, as this area doesn't receive the same dose of chemotherapy as the rest of the body. People undergoing scalp hypothermia report feeling uncomfortably cold and having headaches [27-31]. A number of inhibitive measures have been proposed and tried in an effort to limit chemotherapy-induced hair loss. Of the treatments investigated thus

far, scalp cooling (hypothermia) has been the most widely used and studied, though most published data on this method are of poor quality. Of the 53 multiple patient studies published between 1973 and 2003 on the results of scalp cooling for the prevention of chemotherapy-induced hair loss, seven [27, 32-37] of these trials were randomized. In six [27, 32, 33, 35-37] of the seven randomized studies, a significant advantage was observed with scalp cooling. The favorable results were most evident when anthracyclines or taxanes were used as the chemotherapeutic agents. Some studies have raised concerns about the risk of scalp skin metastases after cooling [38, 39]. Currently, scalp cooling is contraindicated for those with hematological malignancies and its use is controversial in patients with non-hematological malignancies who undergo curative chemotherapy [40]. Patients undergoing scalp hypothermia commonly report feeling uncomfortably cold and experience headaches

Minoxidil (Rogaine). Applying minoxidil a drug approved for hair loss in men and women to the scalp before and during chemotherapy isn't likely to prevent the hair loss, although some research shows it may speed up the hair regrowth. Minoxidil decreased the duration of alopecia caused by chemotherapy. There were no significant side effects. More research is needed to understand whether minoxidil is effective in regrowing hair after cancer treatment [40-43].

An invitro study done by Katikaneni R to investigate PTH-CBD, a collagen-targeted parathyroid hormone analog, in a non-depilated mouse model as prophylaxis of alopecia induced by chemotherapy, his result was optimized, he concludes that PTH-CBD was effective in both the prevention and the treatment of chemotherapy-induced alopecia in mice, but pretreatment appears to result in a better cosmetic outcome. PTH-CBD shows promise as an agent in the prevention of this complication of chemotherapy and improving the quality of life for cancer patients [44].

Propranolol is a non-selective  $\beta$ -blocker developed in the 1950s by Sir James Black, who was awarded the 1988 Nobel Prize in Medicine was the first  $\beta$ -adrenergic receptor antagonist found to be useful in clinical medicine [45]. Propranolol is a beta-blocker. Beta-blockers affect the heart and circulation (blood flow through arteries and veins). Mechanisms, such as vasoconstriction, endothelial cell apoptosis and decreased angiogenesis, have been proposed to explain how propranolol affects IHS, although the exact mechanism remains unclear.

Propranolol is generally a safe drug, but it has been associated with adverse events such as bradycardia, hypotension, hypoglycemia, and bronchospasm [46]. Lawley et al described a case in which a neonate taking propranolol had a critically low serum glucose level while being completely

asymptomatic. They suggested that the  $\beta$ -blockade most likely caused the child to be asymptomatic and, for this reason, they recommended caution in the widespread use of propranolol [47]. Some authors recommend that all patients should have electrocardiograms and echocardiograms before commencing propranolol therapy to rule out contraindications to  $\beta$ -blockade) [46, 47]. Slow upward titration of the drug and close monitoring of heart rate, blood pressure, and serum glucose levels have also been recommended in the initial phase of treatment [46, 47].

Beta blockers inhibit vasodilatation, which leads to immediate changes in the IHS, due to decreased blood flow from the capillaries feeding the IH and can be observed as color lightening and softening within the first 3 days of initiating treatment. Angiogenic growth factors are important in endothelial cell proliferation. Beta blockers are proposed to downregulate angiogenic growth factors, such as vascular endothelial growth factor (VEGF-A), matrix metalloproteinases (MMP-2 and MMP-9) and interleukin 6 (IL-6) [48].

propranolol may block phosphorylation of vascular endothelial growth factor receptor 2 (VEGFR-2) [46]. It was found that when hemECs were challenged with higher concentrations of propranolol (50 and 100 mmol/L), the expression of VEGF at the protein level was reduced in a dose-dependent manner [49, 50]. This reduction in the level of activated VEGFR-2 receptors and VEGF protein upon propranolol exposure was a critical element that affected the survivability of these hemECs [46, 51]. In addition, the decrease in key cyclin levels and an increase in cell cycle inhibitor levels were observed [46]. This suggested that cell cycle regulation is also another mechanism involved in mediating propranolol's therapeutic effect. HemECs show a greater proportion of cells in the G1 phase than the S/G2 phase when treated with propranolol [46]. This was further confirmed by decreased expression of cyclin proteins such as cyclins A1, A2, B2, D1, D2, D3,29,50,52 while cell cycle inhibitor proteins p15, p21, p27 were upregulated [46, 52].

propranolol has another unusual mechanism that clarifies in a study by Wolter in 2012 that review that propranolol treatment in vitro is associated with induction of apoptosis and the pro-apoptotic p53 family proteins p53 and p73 (regulatory cycle genes). Propranolol reduced cell viability and induced apoptosis. In response to propranolol,  $[\Delta]Np63[\alpha]$  decreased, whereas TAp73 $[\beta]$  and downstream proapoptotic p53 family target genes increased. Expression of the proangiogenic protein vascular endothelial growth factor (VEGF) also decreased [53].

Using propranolol as treatment for hemangiomas is unusual use. In 2008, a group of physicians from Bordeaux Children's Hospital in France described an interesting observation from several patients with extensive infantile hemangiomas<sup>10</sup> who received concomitant treatment with propranolol (for obstructive hypertrophic cardiomyopathy and high cardiac output). In each case, the hemangioma regressed upon initiation of propranolol and the children were eventually weaned from corticosteroids without recurrence of hemangioma growth [54]. In the same article, the authors also described similar findings in 9 other children with substantially large hemangiomas whom they treated with propranolol. In a follow-up report, 32 children with complicated hemangiomas treated with propranolol experienced immediate colour changes and effects on growth in all cases [55], with only one patient discontinuing the drug owing to respiratory wheezing. The mechanism of action of propranolol is unclear. It is hypothesized that as a  $\beta$ -adrenergic antagonist it induces vasoconstriction, resulting in colour change and palpable softening of the hemangioma, even within 24 hours of treatment [54], or that propranolol might cause downregulation of growth factors, such as vascular endothelial growth factor, and up-regulation of cellular apoptosis [45,54]. The doses of propranolol that used in capillary hemangioma as topical are propranolol 1% to 3% applied topically 2 to 4 times daily; 1% twice daily was the most frequently used protocol. Duration of therapy ranged from 5 weeks to 17 months; optimal duration unknown (Off-label dosage) [26].

Unlabeled use of propranolol like using it for decreasing the proliferation of endothelial cells transformed by Kaposi's Sarcoma-Associated Herpesvirus and inducing Lytic Viral Gene Expression [56], it is approved as a generic  $\beta$ -adrenergic antagonist, decreased proliferation of KS-associated herpesvirus (KSHV)-infected cells. Downregulation of cyclin A2 and cyclin-dependent kinase 1 (CDK1) recapitulated this phenotype. Additionally, propranolol induced lytic gene expression in association with downregulation of CDK6. Thus, propranolol has diverse effects on KSHV-infected cells, and this generic drug has potential as a therapeutic agent for KS. Like KS, the vascular lesion infantile hemangioma (IH) develops from the dysregulated proliferation of EC [57]. The generic  $\beta$ -adrenergic antagonist propranolol has been shown recently to be effective against IH and is now a first-line agent for treatment of this vascular lesion [58, 59]. Given the similarities between KS and IH, we hypothesized that propranolol would decrease proliferation of KSHV-infected EC in a validated in vitro KS model [60]. Here we show that postconfluent growth of EC transformed by KSHV requires cyclin-dependent kinase 1 (CDK1) and one of its binding partners, cyclin A2, to complete the S and G2-M phases of the cell cycle. Furthermore, we show that induction of KSHV lytic gene expression is associated with

downregulation of CDK6. These data suggest that adrenergic signaling drives KS cell proliferation and suppresses viral reactivation in part by maintaining high levels of cyclin A2 and CDK6, respectively. Additionally, these data identify propranolol as a potential agent for treatment of KS amenable to use in limited-resource settings.

In vitro study in 2009 put a spot about the role of propranolol as a protective agent in pancreatic cancer by inhibition of cAMP. These findings further highlight the importance of cAMP signaling downstream of  $\beta$ -ARs in the regulation of pancreatic cancer [61].

So propranolol has some controlling effect on biomolecules cyclin-dependent kinase 2 (CDK2) and P53 that sharing in cell cycle proliferation.

### **In summary**

The strategy that protects against chemotherapy-induced hair loss may involve arresting the cell cycle in order to reduce the sensitivity of the follicular epithelium to cell cycle active antitumor agents. Inhibition of cyclin-dependent kinase 2 (CDK2), a positive regulator of the eukaryotic cell cycle, may represent a potential approach that arrests the cell cycle. Potent small-molecule inhibitors of CDK2 are currently being developed using structure-based methods [4]. With more clarification attempting to control the hair phases to be all in resting phase (catagen phase) by controlling cell hair dividing under the pharmacological mechanism of propranolol may be will help to prevent the chemotherapy induced alopecia.

Propranolol confirmed with decreased expression of cyclin proteins such as cyclins A1, A2, B2, D1, D2, D3,29,50,52 while cell cycle inhibitor proteins p15, p21, p27 were upregulated [46, 52].

Another strategy that protects against chemotherapy-induced hair loss. Rapid inhibition of P53 (Cycle-regulating genes) activity in hair-follicle stem cells via increased MDM2 expression promotes survival of hair-follicle stem cells after DNA damage [18].

Propranolol treatment in vitro is associated with induction of apoptosis and the pro-apoptotic p53 family proteins p53 and p73 (regulatory cycle genes). Propranolol reduced cell viability and induced apoptosis. In response to propranolol,  $[\Delta]Np63[\alpha]$  decreased, whereas TAp73 $[\beta]$  and downstream proapoptotic p53 family (regulatory cycle genes) target genes increased. Expression of the proangiogenic protein vascular endothelial growth factor (VEGF) also decreased [53].

### **CONCLUSION**

In my assumption, there may be a link between the mechanism of action of propranolol as CDK downregulation and p53 and pathophysiology of alopecia induced by chemotherapy

Many trials have been done as a prophylaxis and treatment of chemotherapy induced alopecia invitro and in vivo, but still, no significant treatment can be used, so this is the gap this study will fill it. For my best knowledge:propranolol will have an optimistic future study as the  $\beta$ -adrenergic inhibitors that will be used as a prophylaxis for alopecia induced by chemotherapy.

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