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Present Chemotherapy Induced Alopecia and Research in Future

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Abstract

CIA (Chemotherapy Induced Alopecia) is a common side effect seen during cancer treatment and a distressing symptom in many types of cancer patients. Patients exposed with alopecia during cancer treatment were accompanied by social influences and further quality of life. Although hair regrows in 3-6 months after chemotherapy, the regrown hair has changes in color, structure, texture etc. In the United States, chemotherapeutic patients had alopecia in varying degrees, where woman patients considered CIA as the most severe trauma, and even refused proper chemotherapy or have chosen an alternative therapy. Furthermore, the reported conditions of permanent CIA have been increasing. The CIA measures are mainly assessed using NCI-CTCAE, CTC, WHO, and GPA. Etiologically, CIA might be caused by therapeutic agents, genes and hormones. Diagnosis includes CST (Cross-Section Trichometry), Trichoscopy and OCT (Optical Coherence Tomography). Currently, the mainly reported used prevention of CIA is scalp cooling, and FDA has classified the scalp cooling system into class II (special controls) to provide a reasonable assurance of safety and effectiveness of the device. Scalp cooling is influenced by temperature, therapeutic agents, time and physiological factors. Besides physical interventions, several novel methods have been reported in animal models recently including drug-specific antibodies, hair growth cycle modifiers, cytokines, growth factors, antioxidants, cell cycle/proliferation modifiers or inhibitors of apoptosis, LLLT (Low-Level Laser Therapy), many drug preventions being under preclinical research. Thus, this review explores the current clinical treatment and future researches.

Keywords: Chemotherapy induced alopecia; Hair follicle; Stem cell; Scalp cooling; Chemotherapeutic agents

Introduction

Chemotherapy is a common cancer treatment (occurs in 65% [1]) that inevitably brings some side-effects, such as nausea-vomiting, fatigue-weakness, anxiety-depression, hyperglycemia-diabetes mellitus etc. [2,3]. Alopecia is a common skin disease, especially in patients with neoplastic medical behaviors [4], affecting both males and females and all age groups [5]. CIA (Chemotherapy-Induced Alopecia) is frequently described as one of the most distressing aspects of cancer treatments [6]. Patients exposed with alopecia during cancer treatment were accompanied by social influences such as social, physical and psychosocial well-being, self-confidence, sadness, and further quality of life [7]. 47-85% woman patients considered CIA as the most severe trauma, and as many as 10% patients have refused proper chemotherapy or have chosen an alternative therapy [8].

Clinical Manifestations

The average incidence of hair loss in cancer patients was approximately 65%. CIA is generally a temporary condition, wherein the hair regrowth occurs after 3-6 months following the treatment. Additionally, hair re-growth after chemotherapy showed a different color, structure, texture, growing speed and low density [6]. A pediatric study reported that hair re-growth post-chemotherapy was accompanied by reduced hair density (67.1% patients) or changed hair density (45% patients). Patients' hair changes were demonstrated by hair color change in 58.3%, lighter hair weight in 79.8%, altered hair texture in 78.8%, and thinner hair in 80.8% patients [9]. Since only pediatric data was reported till now, our next research is to investigate the situation in adults.

Number of PCIA (permanent CIA) reports has been increasing continuously and is defined as incomplete hair re-growth for >6 months after chemotherapy [10]. PCIA possibly results from irreversible hair follicle stem cell destruction in the hair bulge. (The bulge is located in the outer root sheath at the insertion point of the arrector pili muscle. It houses several types of stem cells, which supply the entire hair follicle with new cells, and take part in healing the epidermis after a wound), or disruption of signaling to the secondary hair germ [11] (Hair germ is a hair follicle primordium in embryonic/perinatal mammalian skin associated with the epidermis [12]). PCIA has been reported to be associated with several drugs, for example busulfan-cyclophosphamide combination therapy, which acts as a conditioning regimen prior to bone marrow transplantation, and chronic graft-versus-host disease, and PCIA has also been reported following the use of cyclophosphamide, melphalan, thiotepa, carboplatin, docetaxel, paclitaxel, tamoxifen and alfa-2a interferon [13,14]. Also, other body sites that might be influenced during chemotherapy include eyebrows, eyelashes, axillary and pubic hair

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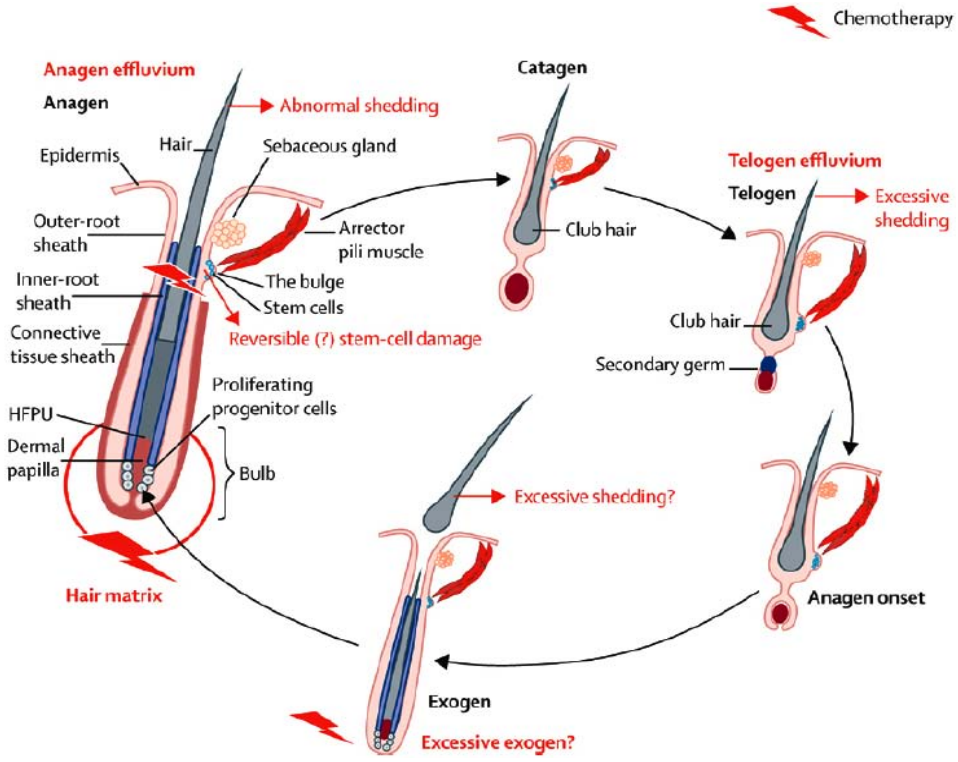

Figure 1: Effects of Chemotherapy on Human Hair Follicle.

[10].

The CIA measures are mainly assessed using NCI-CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events), CTC (Common Toxicity Criteria), WHO (World Health Organization), and GPA (Global Photographic Assessment) [15].

Cause of Hair Loss

There are many cancer therapeutic agents that cause CIA. However, many studies have reported but were less focused, while very few reports discussed on the relationship, mechanism and influence between agents and alopecia. Gulbeyaz Can et al. [16] have reported the CIA incidence and its effects on body image, quality of life. They analyzed cisplatin-based, taxane-based, fluorouracil-based, and doxorubicin-based therapy and other chemo regimens; concluded taxanes were important factors affecting the body image, though the conclusion was merely restricted within Turkish cancer patients. Another report on permanent alopecia has divided patients into three groups (chemotherapy or radiation or both). Oral serum busulfan, Docetaxel, carboplatin, thiotepa and tamoxifen can cause PCIA [10]. Other reports on therapeutic agents included: cyclophosphamide, daunorubicin, epirubicin [8], platinum compounds [17], 5-fluorouracil [14], and etoposide [18]. Generally, the highest incidence of CIA takes place in breast cancer patients [17].

Similar to other diseases, alopecia is also related with confidential genes. Chung et al. [19] reported that CIA is strongly associated with genetic variants near gene CACNB4 and with SNPs. They also reported CIA-associated genes in GWAS (Genome-Wide Association Study). This conclusion provided new view and direction on CIA pathogenesis, and those related cytokines that regulates these gene expressions provided novel treatment as well as prevention research direction. Women with genetic predisposition or family history usually had alopecia [20].

Tumors can be divided into dependent or independent to hormone types. Endocrine therapy is gradual in effect, mild in toxicity, used in the two kinds of tumors. Hormone Replacement Therapy (HRT) has proven to be highly effective in alleviating menopausal symptoms and in preventing osteoporosis. According to preclinical data, estrogen and progesterone are supposed to be involved in the induction and progression of breast and endometrial cancers [21]. Aromatase inhibitors are frequently-used therapeutic agents for low estrogen concentration and higher androgen concentration. A cross-sectional study analyzed 851 female breast cancer survivors who responded to a hospital registry-based survey in the Mercy Medical Center, suggesting that both alopecia and hair thinning are linked to aromatase inhibitors [22]. Tamoxifen, toremifene, medroxyprogesterone, megestrol, abiraterone, flutamide, bicalutamide are also reported in CIA [23,24]. Growth hormone stimulating insulin-like growth factor-1 secretion also plays a role in promoting hair cycle. Low levels of estrogen associated with different kinds of hair loss. Effects of chemotherapy on human hair follicle growth cycle mainly on bulb at the bottom (Figure 1) [25].

Clinical Prevention

Scalp cooling: Currently, the mainly reported used prevention of CIA is scalp cooling, and FDA has classified the scalp cooling system into class II (special controls) to provide a reasonable

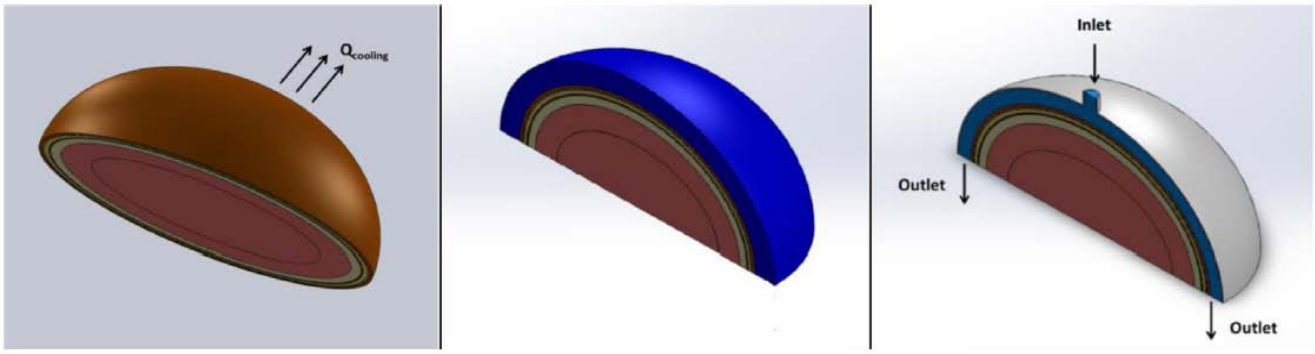

Figure 2: External Cooling Sources.

assurance of safety and effectiveness of the device. Cold temperature with vasoconstriction causes hair follicles to assimilate less with therapeutic agents, also reduces metabolism of tissues and cells', wherein less agents enter into the hair follicle cells, decreasing the chemotherapeutic effects to hair. Clinically, doxorubicin, epirubicin or docetaxel in solid tumors, especially breast cancer and that contra indicatory in hematological malignancies such as scalp metastases, abnormal liver function, imminent bone marrow-ablation chemotherapy and imminent skull irradiation were suggested for scalp cooling [26-28]. Commonly, external cooling sources contain three kinds: uniform heat flux (left), pre-cooled cap (center),and liquid-cooled cap(right) (Figure 2) [29].

Pulsed electrostatic fields and scalp tourniquets (a kind of special bands that tightly fit the scalp region to occlude the superficial blood flow and thus reduce the amount of drug delivered to the HFs [30]) are also used to prevent CIA [22]. Besides physical interventions, several novel methods have been reported in animal models recently including drug-specific antibodies, hair growth cycle modifiers (e.g. epidermal growth factor), cytokines, growth factors, antioxidants, cell cycle/proliferation modifiers or inhibitors of apoptosis [31].

Prostaglandin F2α analogs showed potential benefits of treating different kinds of alopecia, including CIA, wherein the prostaglandin F2α analogs can activate anagen phase and melanogenesis in the skin. Prostaglandin analogs (such as Bimatoprost) are the only possible treatment for hypotrichosis and alopecia of the eyelashes [32]. US FDA approved Minoxidil was reported that the topical application of 2% minoxidil gives rise to early recovery from CIA in some breast and gynecological cancer patients with special therapeutic agents. Calcitriol is effective in DNA synthesis inhibition and cell differentiation, which was verified to prevent special agents that induced hair loss in animal model [33]. However, similar to minoxidil, obvious preventative efficacy in humans has not been observed.

JAK (Janus Kinase) inhibitors represent a promise among alopecia treatments [34]. Additional evidence suggests that JAK inhibition might be broadly useful in dermatology, with early reports of efficacy in several other conditions, including chemotherapy induced alopecia [35]. Free radicals damage hair follicles, and so free radical inhibitors may be effective in CIA prevention [36]. Still, these studies are in the basic research or in animal model stage.

Alternative chemotherapeutic regimen, including all-oral NORCAP (vinorelbine/capecitabine) to replace the first-line taxanes, and dactinomycin or carboplatin for second-line treatment of methotrexate-resistant low-risk disease, is another choice to avoid CIA [37]. Of course, changing chemotherapy regimen depends on whole assessment of treatment efficacy and settings (such as cure vs palliative). A CIA literature collection revealed LLLT (Low-Level Laser Therapy) stimulated the epidermal stem cells and shifting the follicles into the anagen phase, and proved safety and effect for hair growth in patients [38].

Researches on CIA

PCIA is usually caused by toxic damage to stem cells in the hair bulge or from disruption of signaling to the secondary hair germ [11]. The main reasons include stem cell destruction, matrix keratinocyte damage, especially bulge damage of hair follicle stem cells. The p53 protein is essential for CIA, as it mediates apoptosis and growth arrest in TP53-negative cancers [10]. Targeting p53 protein or hair follicle stem cells are potential for the prevention of CIA. Small molecular compounds on targeting TLR7 is under reseach [39]. Hair growth is also mediated by several pathways. Sonic Hedgehog (Shh) signaling pathway inhibition results in the reversible hair loss and ceases hair growth at telogen phase. EGFR inhibition is vital in anagen-catagen transition, resulting in the follicular disintegration accompanied by inflammation. These above findings are attested by several case reports. Murine studies demonstrated that FGF (Fibroblast Growth Factor) signaling stimulated hair growth. PDGF signaling induced and maintained hair follicles in the anagen phase [40].

To better manage CIA and study scalp cooling, objective parameter such as HMI should be included in the demographic data of patients' as in standardized registry. Further study should collect more information such as evidence-based data, costs, patient psychological and physical feelings, and more side-effects [15]. At this point, CIA management and measurement should be reevaluated, and also the new standards should be discussed with a clinical specialist. CIA is caused by hair follicle vasculature and sebaceous gland damage [9]. Hence, it needs a larger-scale epidemiological study to identify the relationship between CIA and various factors to provide a more precise research direction.

The used targeted antitumor agents will subordinate chemotherapy (these kinds of patients will suffer from less CIA) [41]. Studies on CIA protective agents or solutions will bring new visual angles into the

drug discovery and study on stem cells. To develop a more precise targeting drug is a new fundamental solution to prevent CIA. Drug discovery is directed to modulators on hair growth signaling pathways, hair follicle cycling and hair follicular stem cell proliferation. Hair follicle neogenesis is a new discovery in the field of CIA. PPR (PTH/PTHrP receptors) agonists and inhibitors were shown to greatly impact on hair growth both *in vivo* and *in vitro*. PPR inhibitors inspire hair follicle cell proliferation. PPR ligands are considered to be potentially safe and effective for treating CIA [42]. Modulation on intrafollicular ABC (ATP-binding cassette) transporters may protect hair follicle stem cells from chemotherapeutic damage, providing a new method for CIA drug research [43]. α-MSH (α-Melanocyte-Stimulating Hormone) is studied as a CIA-protective candidate agent, as it exogenously protects the damage of hair follicles from 4-HC (4-hydroperoxy-cyclophosphamide) in four different female individuals [44]. This result needs further mechanical and clinical research on the potent cell regulators.

Conclusion

In conclusion, CIA (Chemotherapy-Induced Alopecia) is frequently described as one of the most distressing aspects of cancer treatments, especially in woman patients, and is considered very psychological difficult to manage. Besides, the condition of permanent CIA is increasing. Successful CIA treatment can improve patient prognosis, psychosocial well-being, self-confidence, sadness, and further quality of life. The urgent needs for CIA treatment require a new whole clinical insight into CIA. This review provided efficient solutions and research directions on the hair follicle growth factors.

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