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Chemotherapy-Induced Alopecia

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Few dermatologic conditions carry as much emotional distress as chemotherapy-induced alopecia (CIA). The prerequisite for successful development of strategies for CIA prevention is the understanding of the pathobiology of CIA. The incidence and severity of CIA are variable and related to the particular chemotherapeutic protocol. CIA is traditionally categorized as acute diffuse hair loss caused by dystrophic anagen effluvium; however, CIA presents with different clinical patterns of hair loss. When an arrest of mitotic activity occurs, obviously numerous and interacting factors influence the shedding pattern. The major approach to minimize CIA is by scalp cooling. Unfortunately, most published data on scalp cooling are of poor quality. Several experimental approaches to the development of pharmacologic agents are under evaluation and include drug-specific antibodies, hair growth cycle modifiers, cytokines and growth factors, antioxidants, inhibitors of apoptosis, and cell-cycle and proliferation modifiers. Ultimately, the protection should be selective to the hair follicle; for example, topical application, such that the anticancer efficacy of chemotherapy is not hampered. Among the few agents that have been evaluated so far in humans, AS101 and minoxidil were able to reduce the severity or shorten the duration of CIA, but could not prevent CIA.
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Few dermatologic conditions carry as much anxiety and emotional distress as hair loss resulting from chemotherapy-induced alopecia (CIA). CIA is considered one of the most traumatic factors in cancer patient care and occurs with an estimated incidence of 65%. Hair loss negatively affects a patient's perception of appearance, body image, sexuality, and self-esteem. Moreover, patients feel deprived of their privacy because the hair loss is readily interpreted by the lay public as associated with having cancer. Women are particularly affected. A survey demonstrates that 47% of female cancer patients consider CIA the most traumatic aspect of chemotherapy, and 8% would even decline chemotherapy because of this fear of hair loss.[1,2] Also, in school-aged children and teenagers, alopecia may result in reduced social interactions.[3] Therefore, understanding and overcoming CIA represents a major challenge, especially for women and children.

The three major and most frequent toxicities of cytotoxic cancer therapy are bone marrow suppression, gastrointestinal disturbances, and alopecia, which are a consequence of direct toxic insult to the rapidly dividing cells of the bone marrow, gastrointestinal tract, and hair follicle, respectively. It is a major characteristic of the anagen hair follicle that the epithelial compartment undergoes proliferation, with the bulb matrix cells showing the greatest proliferative activity in building up the hair shaft. The abrupt cessation of mitotic activity leads to the weakening of the partially keratinized, proximal portion of the hair shaft, a narrowing, and a subsequent breakage within the hair canal. The consequence is hair shedding that usually begins at 1 to 3 weeks and is complete at 1 to 2 months after initiation of chemotherapy.[4] Alopecia becomes noticeably visible after the loss of 50% or more scalp hair. Because normally up to 90% of scalp hair is in the anagen phase, hair loss is usually copious and the resulting alopecia is quite obvious (Fig. 1). CIA usually is reversible, with hair regrowth typically occurring after a delay of 3 to 6 months.[5] In a number of patients, the regrown hair shows changes in color and/or structure and texture. In some cases, the hair density may remain reduced after CIA.

Substantial efforts have led to the development of a number of effective drugs to manage chemotherapy-induced bone marrow suppression and gastrointestinal disturbances. In contrast, progress in CIA prevention and treatment protocols is still lagging, and no effective treatments for CIA are available. A prerequisite for the successful development of applicable strategies for CIA prevention and/or treatment is the understanding of the underlying pathological dynamics of CIA. Research into overcoming CIA has been hampered due to the lack of clinically relevant models.

Pathological Dynamics of Chemotherapy-Induced Alopecia

In early studies, Crounse and van Scott[6] looked at the effects of cancer chemotherapy agents on hair. With high doses of chemotherapy, they found that hair may be easily epilated in 1 or 2 weeks, followed by a diffuse spontaneous hair loss. The usual change in the hair root is quite characteristic and consists of sharp thinning or constriction, at which point the hairs simply separate. With lower

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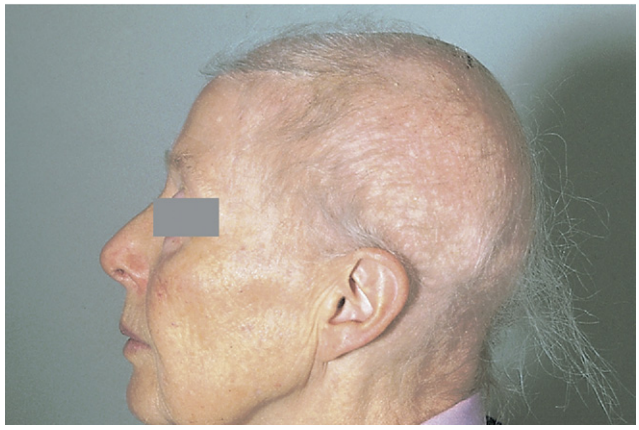

Figure 1 Chemotherapy-induced alopecia (from Trüeb[40]).

doses, there may be only a segmental thinning or narrowing without fracture of the shaft at the point of weakness. When the drug is stopped, the follicle resumes its activity within a few weeks, having experienced no more than a temporary arrest in its growth. Another course of the drug will reproduce these changes. Even when these events are re-enacted many times by repeated courses of therapy, hair growth is only temporarily inhibited. After the hair has regrown, the telogen count is found to be the same even after repeated episodes of hair loss, showing that the hair cycles have not been materially altered.

Kligman[7] followed a group of cancer patients who received high-dose cyclophosphamide intravenously within a period of a week or less and found the effects on the hair to be precisely those described earlier. Histologically, there was a reduction in the volume of the hair bulb reflecting loss of epithelial cells, nonetheless the hairs continued in anagen. It is worth emphasizing that, in this instance, hairs are shed from anagen follicles, so-called anagen effluvium. In all other known instances of reversible hair loss, including androgenetic alopecia, takes place from telogen follicles, so-called telogen effluvium.

The clinical presentation of chemotherapy-induced anagen effluvium differs from the more common type of telogen effluvium. Because up to 90% of scalp hair is in anagen at a given time, and anagen effluvium is not dependent on the transition from anagen to telogen with subsequent release of telogen hairs, hair loss is copious (80%-90%) and occurs within days to few weeks of the causative event. In contrast, telogen effluvium has a latent period of months, and the hair loss is usually subclinical and involves less than 50% of hairs. Besides cancer chemotherapy, other known causes of anagen effluvium include X-ray exposure, exposure to toxins (heavy metals, plant toxins), and immunologic injury caused by the cytokines generated by the peribulbar lymphocytic infiltrate in alopecia areata. All of these, as different as they are, have one thing in common which explains the exceptional phenomenon of anagen effluvium. They stop the reproduction of matrix cells. Evidently mitotic inhibition alone is not sufficient to force the follicle into catagen; it merely causes the follicle to suspend operations. Presumably, the induction of catagen, normally or under pathological conditions, is controlled by forces acting through the hair papilla rather than directly on the follicular epithelium.

Nevertheless, experimental evidence also exists in the literature that the hair follicle may respond to the same insult capable of stopping mitosis with both shedding patterns, (dystrophic) anagen effluvium, and telogen effluvium: Braun-Falco[8] demonstrated, after X-ray administration, the occurrence of an early, severe, and transitory dystrophic anagen effluvium with a longer-lasting telogen effluvium developing later.

Rebora[9] more recently pointed out that when mitotic activity is arrested, numerous and interacting factors influence the shedding pattern: One of these factors is the mitotic activity of the hair follicle at the moment of the insult. Arresting mitosis when the hair is in its highest mitotic rate phase, the arrest of mitosis causes differentiation to stop, producing a sharp constriction of the hair shaft and, therefore, its fracture. When the hair is in its late anagen phase, in which the mitotic rate is slowing down spontaneously, it simply accelerates its normal path to telogen. Finally, mitotically inactive phases (catagen and telogen) are not affected.

The intensity and duration of the antimitotic insult are also important. The incidence and severity of the hair loss are variable and related to the particular chemotherapeutic protocol. Multiple classes of anticancer drugs induce alopecia, with frequencies of CIA (Table 1) differing for the four major drug classes: more than 80% for antimicrotubule agents, for example, paclitaxel; 60% to 100% for topoisomerase inhibitors, for example, doxorubicin; more than 60% for alkylators, for example, cyclophosphamide; and 10% to 50% for antimetabolites, for example, 5-fluorouracil plus leucovorin. Combination therapy consisting of two or more agents usually produces greater incidences of more severe CIA compared with single-agent therapy.

The scalp is the most common location for hair loss; other terminal hairs are variably affected depending on the percentage of hairs in anagen. Chemotherapy given at high doses for a sufficiently long time and with multiple exposures may affect all the beard, eyebrows, eyelashes, axillary, and pubic hairs.

Once the insult is removed, regrowth is usually prompt because normal anagen growth has been only temporarily interrupted. However, permanent alopecia has been reported after chemotherapy with busulfan after bone marrow transplantation[10,11] and has been associated with risk factors, including chronic graft-versus-host reaction, previous exposure to X-ray, and older age of patients.[12]

Finally, there are circumstances in which telogen effluvium is the more likely choice. The most common circumstance is androgenetic alopecia. In this condition, anagen duration is diminished and, consequently, the probability is increased that the antimitotic insult strikes the hair close to the resting phase. Synchronization of hair cycles also plays a role. The long duration of the anagen phase is the main factor determining the individual hair cycles in humans.

Table 1 Cytotoxic Agents and Hair Loss

Cytostatic agents that usually do cause hair loss	
Adriamycin	Docetaxel
Daunorubicin	Paclitaxel
Etoposide	Ifosfamide
Irinotecan	Vindesine
Cyclophosphamide	Vinorelbine
Epirubicin	Topotecan
Cytotoxic agents that sometimes cause hair loss	
Amsacrine	Vincristine
Cytarabine	Vinblastine
Bleomycin	Lomustine
Busulphan	Thiotepa
5-fluorouracil	Gemcitabine
Cytotoxic agents that rarely cause hair loss	
Methotrexate	Procarbazine
Carmustine	6-marcaptopurine
Mitroxantrone	Streptozotocin
Mitomycin C	Fludarabine
Carboplatin	Raltritrexate
Cisplatin	Capecitabine

Again, in androgenetic alopecia, the hair cycles tend to synchronize due to the diminished duration of anagen. Even a minor antimitotic insult, therefore, may produce marked hair loss.

CIA has traditionally been categorized as acute diffuse hair loss caused by a dystrophic anagen effluvium; however, Yun and Kim[13] have recently pointed out that, in fact, CIA may present with distinct clinical patterns of hair loss with a difference observed between men and women. They offer a somewhat different explanation for their observation, but also come to the conclusion that when the mitotic activity of the hair follicles is arrested, numerous and interacting factors influence the final shedding pattern.

Prevention of Chemotherapy-Induced Hair Loss by Scalp Cooling

Since the 1970s, a number of preventive measures have been proposed and tried to reduce CIA.[14] Of these, scalp cooling has been the most widely used and studied.[15] Scalp cooling is accomplished either with cooling agents applied via a cooling cap that is changed several times or by continuous cooling of the scalp with cold air or liquid. The scientific rationale for scalp cooling in the prevention of CIA is two fold: first, vasoconstriction reduces blood flow to hair follicles during peak plasma concentrations of the chemotherapeutic agent, therefore reducing its cellular uptake; and second, reduced biochemical activity makes hair follicles less vulnerable to the damage of chemotherapeutic agents.

In a recent review, 53 multiple patient studies were published between 1973 and 2003 on the results of scalp cooling for the prevention of CIA.[15] Of these, 7 trials were randomized.[16-22] It is difficult to compare most studies because of differences in patient characteristics, chemotherapy, cooling, and hair loss assessment. Nevertheless, the success of cooling was most apparent in the randomized studies. In six of the seven randomized studies, a significant advantage was observed with scalp cooling.[16,17,19-22] The positive results were most evident when anthracyclines or taxanes were the chemotherapeutic agents.[22-25]

Few studies have been conducted to find out which method of scalp cooling is the most effective. Careful application of the cooling cap might be more important than the cooling system itself, as the contact between the cold cap and the scalp is decisive for achieving the desired scalp temperature. Also, the importance of the degree of hypothermia of the scalp skin has hardly been studied. All the same, Gregory and colleagues[26] found the protective effect against hair loss was best in the group of patients who achieved the lowest intradermal temperatures. Finally, postinfusion cooling time also seems to be relevant for the results of cooling, with higher success rates if, after infusion of cytostatics, the cooling time is 90 minutes or more.[15] Theoretically, the cooling period after infusion of cytostatics should be related to the half-life time of the cytostatics used and their active metabolites.

In several publications, authors have expressed their concerns about the risk of scalp skin metastases after cooling. Witman and colleagues[27] and Forsberg[28] reported patients with mycosis fungoides and leukemia, respectively, in whom they suspected there was a causal relationship between the occurrence of scalp metastases and cooling. Only Lemenager and colleagues[24] and Ridderheim and colleagues[29] looked systematically for the incidence of scalp skin metastases after cooling and did not find an increased incidence. Nevertheless, it has to be borne in mind that their conclusions were based on only a 9-month follow-up period. Currently, scalp cooling is contraindicated for those with hematological malignancies, and its use is controversial in patients with nonhematological malignancies who undergo curative chemotherapy.

Pharmacologic Prevention of Chemotherapy-Induced Hair Loss

At present, no approved pharmacologic treatment exists for CIA. Multiple classes of agents with different action mechanisms of action have been and are being evaluated for the prevention and treatment of CIA on the basis of the current understanding of the pathobiology of CIA both in animal models and in human patients.[14] Ultimately, the protection should be limited to the hair follicle, for example, topical treatments that do not hamper the anticancer efficacy of chemotherapy. Among the few agents that have been evaluated in humans, the immune modulator AS101 and the hair growth promoting agent minoxidil were able to reduce the severity or shorten the duration of CIA but could not prevent CIA. AS101 reduced the severity of CIA in human patients treated with a combination of carboplatin and etoposide.[30]

In clinical trials, 2% topical minoxidil solution shortened the duration of CIA in breast cancer patients receiving adjuvant chemotherapy[31] and in gynecologic cancer patients receiving cyclophosphamide, doxorubicin, and *cis*-platinum.[32] Minoxidil was not effective in preventing CIA in female patients receiving doxorubicin for different types of solid tumors[33]; and failed to induce significant regrowth of hair in busulfan and cyclophosphamide-induced permanent alopecia.[11]

Experimental Approaches to Protection Against Chemotherapy-Induced Hair Loss

Although in vitro systems, such as cell and tissue cultures, can be used to study the effects of chemotherapeutic agents on the hair follicle, in vivo models are preferred due to the complexity of hair growth and cycling. One such experimental model, developed by van Neste and colleagues[34] is the grafting of human scalp skin containing hair follicles onto the skin of nude mice. The more commonly used models in CIA studies are rats or mice without human skin grafts. Because CIA occurs when hair follicles are in anagen, to mimic the human situation, animal models of CIA involve procedures that cause the hair follicles to enter the anagen growth phase.

Two approaches are used for this purpose: the first, introduced by Hussein and colleagues[35] is to use neonatal rats that show spontaneous anagen hair growth, and the second, proposed by Paus and colleagues,[36] is to synchronize the hair follicles in adult mice by depilation. Agents that have been tested in such models include drug-specific antibodies; hair growth cycle modifiers, for example, cyclosporin A, AS101, and minoxidil; cytokines and growth factors, for example, ImuVert, epidermal growth factor, and keratinocyte growth factor (FGF7); antioxidants, for example, *N*-acetylcysteine; inhibitors of apoptosis, for example, M50054 (2,2′-methylene bis); and cell cycle and proliferation modifiers.[14]

Because the rapid cell proliferation of hair follicle keratinocytes during anagen renders the hair follicle susceptible to the toxicity of chemotherapy, one strategy to protect against CIA is arresting the cell cycle to reduce the sensitivity of the follicular epithelium to cell cycle-active antitumor agents. Calcitriol (1,25-dihydroxyvitamin D_3), has multiple effects on keratinocytes, ie, inhibits DNA synthe-

sis, causes cell cycle arrest at the G0/G1 interphase, and induces differentiation. Although it was considered a promising agent for treating CIA, it failed to protect against CIA induced by a combination of 5-fluorouracil, doxorubicin, and cyclophosphamide in breast cancer patients.[37] Finally, inhibition of cyclin-dependent kinase 2 (CDK2), a positive regulator of the eukaryotic cell cycle, is believed to represent yet another approach for prevention of CIA by arresting the cell cycle. Potent small-molecule inhibitors of CDK2 have been developed using structure-based methods. Topical application of these compounds in the neonatal rat model of CIA reduced hair loss at the site of application in 33%-50% of the animals.[38]

Perspectives

The major approach to prevent or minimize CIA is by scalp cooling. Unfortunately, most published studies on scalp cooling are rather small, lack an optimal control group, or have no exact description of the duration and the method of scalp cooling. Side effects of scalp cooling include head-aches, complaints of coldness and/or sensations of discomfort, and feelings of claustrophobia. Although side effects are rarely a reason to withhold cooling, further research to improve tolerance for cooling might improve the results. Patient satisfaction should be the most important criteria for success, since objective assessments are difficult and less significant than patient satisfaction.

Advances have been made in the understanding of the pathobiology of CIA, and several experimental approaches to the development of pharmacologic agents to overcome CIA are under evaluation. In view of the fact that cancer usually is treated with combinations of chemotherapeutics, an effective CIA treatment would likely require agents that are effective for different chemotherapeutics with different action mechanisms. An approach would be to combine different strategies. This also holds true for the newer antitumor protocols. Novel agents with a more tumor-specific molecular target, for example, tyrosine kinase inhibitors that block the faulty signalling pathways, or antiangiogenic agents that impede the tumor blood supply, are still given in combination with the traditional cytotoxic chemotherapeutic agents. Therefore, chemotherapy-induced toxicities, such as CIA remain a challenge in the management of cancer patients.

Finally, variations in patient characteristics must be taken into account, since the pattern of CIA varies in individual patients.[13] When the chemotherapy-induced arrest of mitotic activity of the hair follicles occurs, obviously numerous and interacting factors influence the final shedding pattern. Consequently, the question arises whether further insights into the differential mechanisms by which CIA is caused might be helpful in the development of individual strategies for prevention and treatment of CIA.[39]

The recent improved survival by combinations of traditional chemotherapy and the newer molecular targeting strategies has led to the view that cancer treatment is shifting from cure to long-term maintenance, which further highlights the importance of this quality-of-life issue.

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