Review article

Received: 2023-12-10
Accepted: 2023-12-20

BCCR
2023, No 2, Vol 15 :94-102
www.bccrjournal.com

Chemotherapy Induced Alopecia and Scalp cooling Methods: A review of literature

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ABSTRACT

Chemotherapy-induced alopecia (CIA) is a well-known side effect of chemotherapy that is the most traumatic aspect of treatment for more than half of the patients. Psychosocial stress, decreasing self-esteem, and adverse effects on sexual life are reported due to CIA. It is estimated that 60-85% of individuals who received chemotherapy treatment for cancer experienced some degree of CIA. To prevent CIA, different methods such as scalp cooling, scalp compression, and medical therapies have been introduced. Herein, we provide a review of scalp cooling methods, advantages and disadvantages, requirements, and related papers.

Keywords: Cancer; Chemotherapy; Alopecia; Prevention.

INTRODUCTION:

Chemotherapy is one of the common treatments for cancer patients, which is associated with unpleasant side effects. Chemotherapy-induced alopecia (CIA) is a well-known adverse effect of many chemotherapy medications. Typically, the onset of CIA occurs 2 to 4 weeks after the start of chemotherapy (1). CIA is often one of the most feared side effects of chemotherapy, and more than half of patients consider alopecia to be the most traumatic aspect of the treatment process (2). It has been reported that up to 8% of patients are refusing chemotherapy treatment due to this side effect (3). The pattern of hair loss is different in men and women. Hair loss in women occurs only in the head and face and above the eye line, but it occurs in men in a broader area of the body (4).

In most cases, hair growth resumes within 3 to 6 months after the completion of chemotherapy. But in some patients, permanent hair loss is seen after completion of chemotherapy, which is called irreversible CIA (5, 6). Psychosocial stress, decreasing self-esteem, and adverse effects on sexual life are reported due to CIA (2).

Types of CIA:

If alopecia resolves in 3-6 months after the end of chemotherapy, it is known as "temporary alopecia". "Permanent alopecia" is defined as an absence of, or incomplete hair regrowth, for a time longer than six months after completion of chemotherapy (7).

Incidence and prevalence of CIA:

The incidence and severity of CIA appear to be related to many factors like the half-life of drugs, single or combined therapy, the dose and duration of infusion of the chemotherapy agent, and possibly the condition of the hair (1). It is estimated that 60-85% of individuals who received chemotherapy treatment for cancer experienced some degree of alopecia (7). Based on the literature, about 33-35% of patients reported changes in hair structure and texture after chemotherapy (8).

Methods of assessing hair loss rate:

Three different methods have been used in studies to evaluate the rate of hair loss. The WHO assessment method of hair loss is as follows: 0: no change, 1: minimal hair loss, 2: moderate hair loss, patchy alopecia (piece loss), 3: reversible complete hair loss, 4: irreversible complete hair loss and the need to wear a wig.

The second method has been defined by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE); Grade I: Hair loss less than 50% of normal that is not visible from a distance and can only be determined by careful examination. A different hairstyle may be needed to cover hair loss, but a wig or hairpiece is not necessary for camouflage. Grade II: Hair loss greater than or equal to 50% normal for the individual, which is easily visible to others. The need to camouflage hair loss with a wig or hairpiece has a significant psychological effect on the patient.

Dean's scale modified for chemotherapy-induced hair loss, considers the percentage of hair loss. Grade 0: No hair loss, Grade 1: >0 to ≤25% hair loss, Grade 2: >25 to ≤50% hair loss, Grade 3: >50 to ≤75% hair loss, Grade 4: >75% hair loss.

Prevention modalities of CIA:

To prevent CIA, different modalities have been introduced, such as scalp compression, scalp cooling, and some medications (6, 9-11). According to some case report studies, about 30% of patients treated with Taxane chemotherapy experience persistent and permanent hair loss and the use of 5% Minoxidil topical cream twice a day for 6 months has caused hair to return and re-grow (12-14).

Other complementary treatments have been proposed including the use of L-cysteine as oral gelatin capsules, Caffeine shampoo, oral Ginseng tablets, topical Melatonin solution, topical onion juice solution, and oral zinc tablets (11). It seems that zinc tablets and melatonin topical solution stimulate the growth of hair follicles. Melatonin is notable for its protective and anti-apoptotic effects, which can ensure the functional integrity of non-neoplastic cells, and for its strong antioxidant properties

and ability to actively absorb free radicals. Like human skin, human hair follicles have been shown to synthesize melatonin and express melatonin receptors, and an effect of melatonin on the hair growth cycle has been observed. With regard to in vitro studies on melatonin-mediated hair growth stimulation, a double-blind, placebo-controlled experimental study investigated the use of topical melatonin in women with androgenic alopecia, and the results showed a significant increase in detectable anagen hair in the occipital and forehead regions after six months; compared to placebo (15). A clinical trial has reported the usefulness of Coffee shampoo in preventing androgenic hair loss. The possible mechanisms are stimulating keratinocyte proliferation and neutralizing testosterone-enhanced TGF-B2 protein expression in hair follicles (16). L-cystine, a natural compound of keratin, may promote hair growth as an external supplement. An animal study in mice has shown that simultaneous oral administration of L-cysteine and vitamin B6 is effective in preventing hair loss caused by chemotherapy with Doxorubicin (17). Topical solution onion juice stimulates hair regrowth with produces a mild dermatitis (18).

One of the oldest methods is scalp compression which uses a set of round rubber bands or compression devices to compress the scalp mechanically to decrease local blood flow through the vessels, thereby slowing the transport of the cytostatic agent to the hair follicle area. Even though this method was moderately effective, however, it has been performed in a small group of patients without randomization (19).

Among the mentioned methods, scalp cooling is the best-studied; and the only one with proven effectiveness in humans. Herein, we provide a review of scalp cooling methods, advantages and disadvantages, requirements, and related papers.

Cooling techniques:

The method of cooling the scalp to reduce CIA was introduced in the 1970s, which first gained acceptance in Europe and then in the United States (20). Several techniques have been used to induce hypothermia: cold air, bags with crushed ice, frozen cryogel packs or frozen packs with an endothermic cooling reaction, special caps with a layer of thermal insulation, and caps attached to a cooling device using air or fluid as the medium and equipped with a thermostat.

All techniques are categorized as two main scalp cooling methods: cold caps (manual cooling systems including Penguin Cold Caps, Chemo Cold Caps, and Arctic Cold Caps) and scalp cooling systems (automated cooling systems). Manual techniques can be performed using hand-held cold caps, which consist of shower cap-like head coverings that require frequent cooling during treatment to maintain scalp hypothermia. However, machine-based automated cooling systems, which include a tight cap connected to a device that circulates the coolant liquid through the cap, gradually cool the scalp to maintain the set temperature during the treatment. Figure 1 shows two types of scalp cooling methods.

1. Mechanism of Cooling

Scalp cooling prevents CIA via two mechanisms: first by limiting blood flow to the hair follicles during treatment, thereby reducing exposure to chemotherapy agents second by slowing the metabolic rate of the hair follicles; which may reduce their sensitivity to the harmful effects of chemotherapy (9, 20-23).

2. Advantages & Disadvantages

2-1. Advantages

Using a cold cap reduces hair loss and eliminates the need for a wig. The likelihood of a patient who uses scalp cooling during chemotherapy to maintain enough hair to not require a wig is approximately 50% (24). Using cold caps and reducing hair loss strengthens the patient's self-confidence and maintains the individual's image of themselves, creating a positive attitude towards the continuation of treatment, alongside being social.

Comparing the quality of life between people who used cooling caps and the control group shows that people in the first group experience less unattractiveness due to illness and treatment, while the control group is

Figure 1: Left: Paxman Automated cooling machine (https://www.omnia-health.com/product/paxman-scalp-cooling-system), Right: Penguin cold cap (https://penguincoldcaps.com).

dissatisfied with their body and distressed by hair loss (25). Although a systematic review in 2019 evaluating 1282 patients concluded that scalp cooling is not consistently associated with significant quality of life improvements (21).

2-2. Disadvantages

The use of this method has no guarantee that it will be effective for all patients. Failure to prevent hair loss in patients undergoing an expensive and potentially uncomfortable treatment likely contributes to decreased well-being, impacting the overall effects on quality-of-life in scalp-cooling patients.

Adverse effects experienced with scalp cooling were low and similar between studies, including headache, chills, dizziness, skin pain, and itching. These side effects were seen especially in the first 15 minutes. In addition, this method can cause other unpleasant sensations such as nausea, claustrophobia and increased distress (25, 26). However, a large study in Germany showed that only 3% of patients stopped using scalp cooling due to intolerance of the cold, and discomfort of the side effects (27). Some inappropriate side effects can be resolved by covering the patient with an extra blanket, changing the position of patient, and prophylactic use of painkillers (9).

To optimize the use of a cold cap, some measures should be taken before the start of chemotherapy, and after it. Therefore, patients have to stay longer in the hospital, which is inconvenient for some of them.

The last and most important issue regarding the use

of this method, especially in the automatic one, is the cost of scalp cooling. The cost of using a scalp cooling method during chemotherapy is estimated as $1500 to $3000 for each patient (6). Insurance coverage for using this method is another concern that caused many people avoid this method.

3. Literature review

Recent prospective studies have increased our knowledge of scalp cooling techniques and outcomes. Although chemotherapy is commonly used in the treatment of a wide range of malignancies, most of the studies have evaluated the effect of this method on breast cancer patients. In scalp cooling studies generally exclude patients with hematologic malignancies. There has always been a concern that chemotherapeutic agents would be less likely to reach the circulating malignant cells in the cooled area and thus reduce the effectiveness of treatment (28).

One of the concerns with scalp cooling was the potential for scalp metastasis, because the cooling process reduces the level of cytotoxic drugs in the scalp. Various studies have addressed this issue. A study aimed to determine the incidence of scalp metastases among women with primary breast cancer who received neoadjuvant or adjuvant chemotherapy. In this study, a retrospective cohort of women with breast cancer with an average of 5.8 years (±1.7) in the scalp cooling group (553 people) and 5.4 years (±1.7) in the control group (87 people) were followed up. The incidence of scalp metastasis in the cooling intervention group was 1.1% (6 cases out of 553 people) and for the control group, it was 1.2% (1 case out of 87 people). The results of this study showed that there is no statistical difference between the two groups and the incidence of scalp metastases is low (29). Other studies, including the Dutch Scalp Cooling Registry, did not report any cases of scalp metastasis during the 5-year follow-up (27). A systematic review and meta-analysis in 2017 in 1959 patients who were evaluated over an estimated mean time frame of 43.1 months reported that the incidence rate of scalp metastasis in the scalp cooling group versus the no scalp cooling group (0.61% versus 0.41%, P = 0.43) was not statistically different (30). These results show that the concern of an increased rate of scalp metastasis in patients who undergo scalp-cooling is unfounded, and has not been confirmed in any of the studies.

In a large study of the Dutch Scalp Cooling Registry in 28 hospitals, more than 1400 patients treated with chemotherapy and scalp cooling (using Paxman PSC1 or PSC2 systems) were included (27). Overall, 50% of patients did not require a head covering at the time of the last scalp cooling session, although this varied depending on the type of chemotherapy administered (range, 8% to 94%), and the best results were observed in patients who received Taxane monotherapy. In multivariate analysis, patients aged 65 years and older and those with Asian hair type were found to be the most likely to wear headwear at the end of treatment (non-response to treatment). This study supported the effectiveness of scalp cooling and patient satisfaction (27).

Two prospective large studies of scalp cooling have been published in the United States (25, 26). The first study was a multi-center prospective cohort study using the DigniCap scalp cooling device for women (n=122) who received neoadjuvant or adjuvant anthracycline- or Taxane-based chemotherapy for stage I or II breast cancer (25). One-hundred six patients received scalp cooling based on protocol and 14 age- and chemotherapy regimen-matched patients were in the control group. The primary end-point of the study was no hair loss 4 weeks after completion of chemotherapy, which was defined by patient self-assessment using the Dean scale. Secondary end-points included safety and tolerance of treatment, patient satisfaction, and quality of life. In the primary analysis 66% experienced successful hair preservation. The result of this study showed hair loss (equal to 50%) was not affected by hair thickness, previous chemotherapy history, age, body mass index, or previous hormone therapy use (25).

The second study was a multicenter SCALP (head cooling prevention of alopecia) trial of scalp cooling using the Orbis Paxman, in women (n=182) with stage I or II breast cancer who received neoadjuvant or adjuvant

chemotherapy (26). The main objective of this study was to evaluate the effectiveness of this scalp cooling method. Hair loss assessment was according to the Common Terminology Criteria for Adverse Events, Version 4. Hair loss assessment was done by a physician who was unaware of the treatment prescribed for the patient. About 50% hair preservation was observed in the scalp cooling group compared with 0% in the control group. Furthermore, hair preservation was 16% in patients who received anthracycline-based chemotherapy while it was 59% in Taxane-based chemotherapy (26). The results of the two studies mentioned above in similar populations (early-stage breast cancer) were the same and there were no major complications. Both studies showed significant hair preservation with scalp cooling methods, especially in patients undergoing Taxan-based chemotherapy (25, 26).

Other studies have confirmed the effectiveness of cooling systems in preventing alopecia (7, 9, 10, 31, 32). The result of a study investigating the role of cooling agents in preventing alopecia in different chemotherapy regimens showed that treatment with cooling caps was successful 100% and 88% of patients receiving paclitaxel-only and docetaxel-based chemotherapy, respectively. Furthermore, this method was successful in 44% patients when sequential chemotherapy started with anthracyclines and 73% when paclitaxel was administered upfront (33).

With the aim of investigating the survival rate in breast cancer patients who used cooling caps to reduce hair loss, a retrospective cohort study was conducted on 1370 women with non-metastatic invasive breast cancer who received neoadjuvant or adjuvant chemotherapy. A total of 553 women who used scalp cooling were compared with 817 women as controls. The mean follow-up for the scalp cooling and non-scalp cooling groups was 6.3 years and 8 years, respectively. The results showed that there was no difference in overall mortality (34).

Of course, in all studies, the difference in the insulating performance of the scalp structures (hair, dermis and subcutaneous tissue), the amount of heat loss, the anatomy of the skull and the thermal response to vasoconstriction should be considered.

4. Factors affecting the results of a scalp cooling system

4-1. Patient's characteristics

Age, body mass index, sex, race, and other patient's characteristics are factors that are likely to increase the usefulness of the cooling methods. A large multi-center study of Dutch Scalp Cooling Registry in 1411 chemotherapy patients in Netherland concluded besides of type of chemotherapy regimen, dose, and transfusion time; age, sex race, hair length, quantity, chemical manipulation (dyeing, waving, coloring), and wetting hair before scalp cooling are significantly associated with CIA (27). However, another study reported, the incidence of hair loss does not seem to be affected by age, body mass index, hair thickness, and previous hormone therapy use (25).

One study in 2023 in black American breast cancer patients who received scalp cooling showed that this technique may not be efficacious in preventing CIA in black population (35). Hair thickness and volume and limitation of cooling cap design may be the reasons for the ineffectiveness of this method in these patients.

4-2. Cooling duration and temperature

In most studies, pre-cooling time (the time between the start of scalp cooling and the start of intravenous chemotherapy) was between 5 and 30 minutes. However, research on cooling time after injection is scarce. In studies, post-infusion cooling times ranged from 15 minutes to 4 hours (36). It seems that the more acceptable strategy is to start scalp cooling 30 minutes before the chemotherapy infusion, maintaining it during infusion, and then continuing it for 90 minutes after the end of the infusion. The target scalp temperature suggested by Gregory et al during scalp cooling averages about 22°C (37). However, two studies showed that those whose scalp temperature was less than 18 degrees Celsius were likely to have better hair protection (9, 38).

If manual caps are used, it has been suggested that they should be changed three to four times, or every 25 min, during the chemotherapy infusion to ensure a stable temperature (23). However, cooling machines with

thermostat management keep a stable temperature and require fewer nursing interventions (24).

4-3. Chemotherapy drugs

CIA is common in many chemotherapy regimens and the severity of CIA is different in each agent. Notably, scalp cooling failed to prevent alopecia in most patients treated with docetaxel, adriamycin, and cyclophosphamide chemotherapy for primary breast cancer (36). Table 1 shows drugs used for chemotherapy and the severity of alopecia.

4-4. Scalp cooling techniques

Since automatic cooling devices are not available everywhere and the use of manual cooling caps is more cost-effective, some researchers have compared the effectiveness of manual and automatic methods. Betticher et al compared two automatic Paxman scalp cooling systems and manual cold caps and found that both significantly reduced the incidence of CIA, with no difference in efficacy and tolerability (39). Another study that compared the effect of cooling systems and Penguin cap had similar results (40). A recent systematic review and meta-analysis in 2023 with 8 included studies showed a 43% reduction in the risk of CIA (RR= 0.57; 95%CI, 0.50–0.64) after the use of scalp cooling. Moreover, the use of automated scalp cooling devices showed a 47% reduction in the risk of CIA versus a 43% reduction in the risk of CIA for nonautomated scalp cooling devices (41).

Conclusion:

The usefulness of the scalp cooling method has been proven in several studies with low side effects and a high tolerable rate. This method may increase the self-esteem and quality of life in patients who undergo chemotherapy. Prevention of CIA as an unpleasant side effect of cancer therapy encourages patients to continue their treatment. Ideally, the use of scalp cooling should be individualized for each patient. The threshold level of scalp temperature is a critical issue, the timing and technique of scalp cooling must be adapted to individual skin temperature measurements. Factors such as optimal temperature and post-infusion cooling time should be further investigated to advise individual patients on scalp cooling to prevent CIA.

Table 1. Chemotherapy drugs and severity of alopecia caused by them.

Mild alopecia	Moderate alopecia	Severe alopecia
Bleomycin	Busulphan	Cyclophosphamide
Carmustine	Nitrogen mustard	Daunorubicin
Fluorouracil	Floxuridine	Adriamycin
Hydroxyurea	Methotrexate	Vinblastin
Melphalan	Mitomycin	Vincristine
Dacarbazine	Teniposide	Vindesine
Cisplatin	Actinomycin	Ifosphamide
Cytosine arabinosidec	Camptothecins	Etoposide
Thioguanine		Taxoids
Streptozocin		
Chlorambucil		
L-asparaginase		
Thiotepa		
Mercaptopurine		
Hexamethylmelanine		

This table was adapted from the article by Batchelor et al. 2002 (1).

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