

Management of Chemotherapy-Induced Alopecia With Scalp Cooling

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ASSOCIATED CONTENT



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Abstract

Chemotherapy-induced alopecia is a common and distressing adverse effect of many types of chemotherapy. Scalp cooling has been used since the 1970s for prevention of chemotherapy-induced alopecia; however, most data regarding this treatment modality are retrospective in nature, and use in the United States has been limited by safety concerns, specifically the potential for scalp metastases. Two prospective studies of scalp-cooling systems performed in the United States were published within the last year and add evidence supporting the efficacy and safety of scalp cooling in preventing chemotherapy-induced alopecia in patients receiving chemotherapy for solid tumor malignancies. Available data suggest that this technology is most effective for taxane-based chemotherapy regimens compared with anthracycline-based chemotherapy regimens. Two scalp-cooling devices have been cleared by the US Food and Drug Administration, and multiple cold caps are available for patient rental. The adverse effect profile of scalp cooling includes scalp pain, headache, and chills but is tolerable for most patients included in recent clinical trials. Retrospective data suggest that the incidence of scalp metastases related to scalp cooling is low and should not limit use of this technology. Logistic issues related to use of scalp cooling include availability of devices, inconsistent insurance coverage, and incorporation of use into typical infusion center workflow.

INTRODUCTION

Chemotherapy-induced alopecia is a well-recognized adverse effect of many cytotoxic chemotherapy agents. Typically, the onset of chemotherapy-induced alopecia occurs 2 to 4 weeks after the initiation of chemotherapy.¹ Most cases of chemotherapy-induced alopecia resolve within 3 to 6 months after completion of chemotherapy; however, there are cases in which patients have permanent hair loss after cancer-directed therapy, termed chemotherapy-induced irreversible alopecia.^{2,3} Hair loss is often one of the most feared complications of chemotherapy, and it has been reported that up to 8% of patients are hesitant to receive curative-intent chemotherapy because of

concerns centering around chemotherapy-induced alopecia.^{2,4-6} Chemotherapy-induced alopecia is associated with increased psychosocial stress with respect to body image, self-esteem, and sexuality and is common with many chemotherapeutic classes, including anthracyclines, taxanes, and alkylating agents. Various techniques have been used in an attempt to prevent chemotherapy-induced alopecia, including scalp compression, scalp cooling, and medical therapies such as minoxidil and vitamin D3.^{2,7,8} Although each of these techniques has shown promise in animal studies, scalp cooling is the best studied and is the only modality with consistent efficacy documented in humans.



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METHODS OF SCALP COOLING

Scalp cooling has been used for prevention of chemotherapy-induced alopecia since the 1970s, with early adoption in Europe but slow uptake in the United States. Scalp cooling can be accomplished using either manual cold caps, which consist of shower cap–like head coverings that require chilling/freezing and frequent changes throughout therapy to maintain scalp hypothermia, or automatic, machine-based cooling systems, which consist of a tightly fitted cap connected to a device that circulates coolant through the cap and thus gradually cools the scalp to maintain a set temperature throughout treatment. Examples of manual cold cap systems include Penguin Cold Caps (Penguin Cold Caps, London, UK), Arctic Cold Caps (Arctic Cold Caps, Cherry Hill, NJ), Chemo Cold Caps (Chemotherapy Cold Caps, Dallas, TX), Wishcaps (Wishcaps, Cypress, TX), and Warrior Caps (Warrior Caps, Fort Worth, TX). The two machine-based systems are Dignicap (Dignitana, Dallas, TX) and Paxman Scalp Cooling System (Paxman Coolers Limited, Huddersfield, UK). An example of the Paxman Scalp Cooling System cap is shown in Figure 1. Scalp cooling is hypothesized to prevent chemotherapy-induced alopecia by limiting blood flow to hair follicles during treatment, thus decreasing exposure to chemotherapy but also decreasing metabolic rate of hair follicles, which may reduce their susceptibility to the damaging effects of chemotherapy.^{7,9}

Early data on scalp cooling were largely retrospective in nature; however, recent prospective trials have added to our understanding of scalp-cooling techniques and outcomes. Many of the data on scalp cooling come from the breast cancer literature, although the chemotherapeutic agents used in this setting are commonly used in the treatment of a wide range of malignancies. It should be noted that scalp-cooling studies generally exclude patients with hematologic malignancies because of concerns about reducing efficacy of therapy by decreasing chemotherapy delivered to malignant cells circulating in the field of cooling.¹⁰ Scalp cooling should also be avoided in patients with history of cold agglutinin disease, cryoglobulinemia, and cold-induced migraines, because of the potential for exacerbation of these conditions with prolonged exposure to cold temperatures.

SCALP-COOLING STUDIES

The Dutch Scalp Cooling Registry consists of > 1,400 patients treated with chemotherapy and scalp cooling.¹¹ Patients receiving chemotherapy and scalp cooling (using the Paxman PSC1 or PSC2 systems) from 28 hospitals in the Netherlands, including community and academic sites, were asked by nurses



Fig 1. Example of Paxman Scalp Cooling System cap (courtesy of Cleveland Clinic).

to participate in the registry study at the time of treatment initiation. Basic demographic information, treatment regimen, hair characteristics, cooling time parameters, and reasons for discontinuing scalp cooling were recorded. Scalp-cooling treatment was deemed successful if a patient reported not wearing a head cover during their final scalp-cooling session. This was considered a key metric of success of cooling therapy, because it represents patient perception of successful hair preservation rather than objective measurement of hair retention. Severity of hair loss on the standardized WHO scale (0 for no hair loss, 1 for minimal hair loss, 2 for severe hair loss, and 3 for total alopecia) per patient report was also documented.

The vast majority of patients in this study were women who were receiving adjuvant therapy for breast cancer; however, 4% of patients included were men and 14% of patients had malignancies other than breast cancer. As is typical of many scalp-cooling protocols, the median duration of cooling before chemotherapy infusion was 38 minutes, and the median

duration of cooling after chemotherapy infusion completion was 90 minutes. Overall, 50% of patients in the registry did not wear head covering at the time of the final scalp cooling session, although this varied (range, 8% to 94%) depending on the type of chemotherapy given, with best results being observed for taxane monotherapy treatment. In multivariate analysis, patients age ≥ 65 years and those with Asian hair type were determined to have the highest likelihood of having to wear head coverings at the end of treatment. This large registry study provides support for the efficacy of scalp cooling and associated patient satisfaction.

In the last year, two prospective studies of scalp cooling were published in the United States. The first is a multicenter, randomized clinical trial of scalp cooling using the Orbis Paxman Hair Loss Prevention System in women with stage I or II breast cancer receiving neoadjuvant or adjuvant chemotherapy, and the second is a multicenter, prospective cohort study of scalp cooling using the DigniCap scalp-cooling device for women receiving neoadjuvant or adjuvant chemotherapy for stage I or II breast cancer (Table 1).

In the nonblinded SCALP (Scalp Cooling Alopecia Prevention) trial conducted by Nangia et al,¹² patients received scalp cooling or no scalp cooling while undergoing taxane- or anthracycline-based chemotherapy (including the combination of both agents) as neoadjuvant or adjuvant treatment of

early-stage breast cancer. The primary objective of this study was to evaluate efficacy of this method of scalp cooling defined as successful hair preservation after four cycles of chemotherapy. Common Terminology Criteria for Adverse Events version 4.0 grading of alopecia was used with successful hair preservation defined as grade 0 (no hair loss) or grade 1 ($< 50\%$ hair loss, not requiring a wig). Assessment of hair loss was done by a clinician who was unaware of the patient's assigned study treatment. Scalp cooling was done for 30 minutes before chemotherapy, throughout chemotherapy, and for 90 minutes after completion of infusion.

A total of 182 patients were randomly assigned in this study in a 2:1 fashion, with 119 randomly assigned to receive scalp cooling. Results of the study were reported at the time of the first interim analysis, with 95 patients in the scalp-cooling arm and 47 in the control arm evaluable for efficacy analysis. Secondary end points included hair preservation assessed by patient's primary clinician and patient, use of wigs/head wraps, quality of life, and patient-reported comfort. Patients were treated with a variety of chemotherapy regimens in this study, with 36% of patients receiving anthracycline-based treatment and 64% receiving taxane-based treatment.

At the time of interim analysis, 50.5% of the patients in the scalp-cooling group had hair preservation, compared with 0%

Table 1. Comparison of Recent Scalp-Cooling Studies

First Author	Device Used	Cooling Schedule	Study Population	Type of Chemotherapy	Outcomes
Nangia ¹²	Paxman cooling system	30 minutes before treatment, during treatment, and 90 minutes after treatment	Patients with early-stage breast cancer (N = 182)	Taxane or anthracycline based (including both agents sequentially)	51% hair preservation in cooling group 0% hair preservation in control group 59% hair preservation with cooling and taxanes 16% hair preservation with cooling and anthracyclines
Rugo ¹³	Dignicap cooling system	30 minutes before treatment, during treatment, and 90-120 minutes after treatment	Patients with early-stage breast cancer (N = 122)	Taxane based (anthracycline based allowed, but no enrolled patients treated with anthracycline)	66% hair preservation in cooling group 0% hair preservation in control group
Rice ¹⁴	Penguin Cold Caps	Details not specified in publication	Patients with early-stage and metastatic breast cancer (N = 103)	Taxane or anthracycline based (including both agents sequentially)	61% hair preservation overall 50%-84% hair preservation with taxane-based therapy 20%-43% hair preservation with anthracycline-based therapy

of the patients in the control group. Hair preservation success in the scalp-cooling group was found to differ based on chemotherapy type (16% with anthracycline-based chemotherapy v 59% with taxane-based chemotherapy) and varied between study sites, suggesting that success in hair preservation is somewhat dependent on technique of use. Adverse events related to scalp cooling included headache, nausea, chills, dizziness, skin pain, skin ulceration, dry skin, sinus pain, paresthesia, and pruritus. All were grade 1 or 2. The median score on comfort assessment was reasonably comfortable, and one patient withdrew during the first cycle of chemotherapy because of therapy being too cold. Four additional patients withdrew from the study before receiving chemotherapy for this reason during the precooling phase. With respect to quality-of-life end points, there was no difference in emotional functioning, social functioning, and anxiety/depression summary scores between patients in the control group, the scalp-cooling group who achieved hair preservation, and the scalp-cooling group who did not achieve hair preservation. Because the *P* value of the difference in hair preservation ($P < .001$) crossed the predefined superiority boundary, study accrual was stopped early and results of the study were released.

In the prospective cohort study conducted by Rugo et al,¹³ women receiving anthracycline- or taxane-based neoadjuvant or adjuvant chemotherapy for early-stage breast cancer received scalp cooling for 30 minutes before chemotherapy, throughout treatment, and for 90 minutes after infusion. Patients who received combination or sequential taxane- and anthracycline-based treatment were not eligible for inclusion in the study. The primary end point of the study was prevention of hair loss 4 weeks after completion of chemotherapy as defined by patient self-assessment using the Dean scale. A Dean scale score of ≤ 2 (corresponding to hair loss $\leq 50\%$) was considered successful hair preservation. Secondary end points included safety and tolerability of the treatment, patient satisfaction, and quality of life.

A total of 122 patients were enrolled in this study, with 106 in the scalp-cooling group and 16 in the control group. The control group consisted of patients matched for age and chemotherapy regimen with those in the intervention group. This group was intentionally small in size because of the known high likelihood of hair loss ($> 65\%$ incidence) with the chemotherapy regimens included in this study. The most common chemotherapy regimen given to patients in this trial was docetaxel plus cyclophosphamide. Although anthracycline-based chemotherapy was allowed, no patients in the study actually received

anthracycline-based therapy. One hundred one patients from the scalp-cooling group were included in the primary efficacy analysis, and 66% experienced successful hair preservation. Interestingly, the incidence of hair loss $\leq 50\%$ did not seem to be affected by hair thickness, history of prior chemotherapy, age, body mass index, or use of prior hormone therapy. Adverse effects experienced with scalp cooling in this study were similar to those in the SCALP study, including headache, chills, head discomfort, skin pain, and pruritus. Only 3% of patients discontinued study treatment because of discomfort with cold.

In contrast to the SCALP study, differences in certain quality-of-life end points were observed between patients in the cooling and control groups. Patients in the scalp-cooling group were significantly less likely to report feeling less physically attractive as a result of their disease or treatment or being dissatisfied with their body compared with those in the control group ($P = .02$ and $.04$, respectively). Those in the control group were more likely to report being upset about hair loss ($P = .04$).

These two studies included similar patient populations with early-stage breast cancer and had similar results, with a significant proportion of patients achieving hair preservation with scalp-cooling technology, particularly those patients treated with taxane-based chemotherapy regimens. The safety profiles of the techniques were also similar, with no major concerns identified.

A registry study of manual cold cap technology was also recently published. This study assessed efficacy and tolerability of scalp cooling using the Penguin Cold Caps as part of a program to objectively study scalp-cooling devices at the University of California San Francisco.¹⁴ Patients were eligible for participation in this registry study if they were scheduled to receive chemotherapy for breast cancer that would be anticipated to cause alopecia. Hair loss was assessed at baseline, every 3 to 4 weeks during chemotherapy, and 4 weeks after completion of chemotherapy by both patient and medical provider. Successful hair preservation was defined as completion of scalp cooling throughout all planned treatment with $\leq 50\%$ hair loss at all measured time points. If scalp cooling was discontinued because of adverse event or hair loss, this was considered treatment failure.

Ninety-seven patients were evaluable for efficacy of scalp cooling using this cold cap system. As per patient assessment, nearly 61% of patients successfully retained hair during treatment, with the best outcomes occurring in patients who received four cycles of docetaxel plus cyclophosphamide

treatment; nearly 84% of these patients had successful hair preservation. Successful hair preservation with anthracycline-containing regimens in this study varied from 20% to 43%, with better rates of hair preservation in patients who received sequential taxane before anthracycline-based chemotherapy rather than after. Fifteen percent of patients discontinued scalp cooling before completion of therapy, including nine patients who developed hair loss and six patients who had cooling therapy-related adverse effects. Of the patients who completed all planned chemotherapy and cooling therapy, headaches, chills, nausea, and scalp pruritus were commonly reported adverse effects of scalp cooling. Despite these treatment-related adverse events, 100% of patients who completed therapy reported that they would recommend the cold cap system to another patient receiving chemotherapy.

RISK OF SCALP METASTASES AND IMPACT OF SCALP COOLING ON SURVIVAL

Because scalp cooling has primarily been studied in patients receiving curative-intent chemotherapy, there have been concerns raised regarding potential long-term adverse events related to use of this technology. Concern regarding impact of scalp cooling on chemotherapy reaching the scalp and associated risk of scalp metastases has been a significant barrier in assimilation of this technology into routine cancer care. Because the aforementioned US prospective studies are early in terms of length of follow-up, they have limited impact regarding this particular safety concern.

The Dutch Scalp Cooling Registry had up to 5 years of patient follow-up at the time of publication and reported no cases of scalp metastases.¹¹ A large review performed by Grevelman and Breed¹⁵ analyzed 58 publications regarding scalp cooling from 1973 to 2003, and only 24 commented on incidence of scalp metastases. Of these 24 studies, 16 reported no cases of scalp metastases after scalp cooling. The remaining six studies included a total of nearly 2,500 patients, of whom only nine patients (0.36%) were reported to develop scalp metastases, including two patients with hematologic malignancies. This finding is reassuring; however, it is difficult to generalize these results, because the studies included in the review were heterogeneous in terms of type of malignancies and associated chemotherapy regimens, cooling protocol parameters, and length of patient follow-up. Results from another study involving use of the MSC manual cooling cap system (Medical Specialties of California, London, UK) in 442 patients with various solid tumors who received chemotherapy

regimens associated with alopecia found an incidence of scalp metastases in 0.45% in the study population with 7 years of follow-up,¹⁶ consistent with the results of the Grevelman and Breed review.¹⁵ In addition, a 2014 retrospective cohort study of > 1,300 Canadian patients with nonmetastatic breast cancer who received curative-intent therapy showed that overall survival was no different in patients who received scalp cooling compared with those who did not.¹⁷ In total, these studies support the safety of scalp cooling in patients with solid tumor malignancies undergoing chemotherapy.

PRACTICAL CONSIDERATIONS

There are multiple practical issues that need to be considered when implementing use of scalp-cooling technology. One concern is how to incorporate pre- and postchemotherapy scalp-cooling periods into the workflow of an infusion suite. The prechemotherapy cooling period may occur in conjunction with the administration of any necessary prechemotherapy medications, including steroids and antiemetics. If this is done, there should not be any time added to the period of time a patient spends in the infusion suite. The postchemotherapy cooling period could be performed in a waiting room-type area, because patients do not require any further nursing support at that point. The cost of scalp cooling is also a concern for many patients. It is estimated that a full course of scalp cooling during adjuvant chemotherapy costs approximately \$1,500 to \$3,000 per patient.¹⁸ Scalp-cooling treatment is variably covered by insurance, although patient assistance may be available for some patients through the nonprofit organization HairToStay.

In conclusion, both the DigniCap and Paxman Scalp Cooling System have received clearance from the US Food and Drug Administration and therefore are now available for routine use in the United States. Manual cold cap systems are also readily available for purchase or rental, so motivated patients are able to coordinate use of these with chemotherapy. On the basis of the available data, scalp cooling is an effective and generally well tolerated method for prevention of chemotherapy-induced alopecia.

Although there is limited follow-up from the recent prospective studies performed in the United States, documented risk of scalp metastases associated with use of scalp cooling in global retrospective studies is small and should not limit clinician support of patient desire to pursue scalp cooling. Clinicians should be aware of the available data on hair preservation with scalp cooling to counsel patients on the likelihood of success with various chemotherapy regimens. The logistics of widespread use of this technology will ultimately depend on insurance coverage

and impact of device use on overall functioning of chemotherapy infusion centers, especially in light of the time added to treatment of precooling and postcooling periods. Because prevention of chemotherapy-induced alopecia may have an effect on quality of life and psychosocial well-being, use of scalp-cooling technology should be viewed as a means to care for the whole patient rather than a solely cosmetic issue. **JOP**

Authors' Disclosures of Potential Conflicts of Interest

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