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CLINICAL TRIAL

Registry study to assess hair loss prevention with the Penguin Cold Cap in breast cancer patients receiving chemotherapy

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Abstract
Purpose Chemotherapy-induced alopecia is a distressing side effect of cancer treatment. The aim of this registry study was to assess efficacy and tolerability of scalp hypothermia using Penguin Cold Caps (Penguin) in breast cancer patients.
Methods Hair loss was assessed by patients using a 100-point Visual Analog Scale (VAS) and by physicians using the 5-point Dean Scale at baseline, every 3–4 weeks during chemotherapy, and at least 1 month after completion of chemotherapy. The primary efficacy endpoint for success was defined as ≤50% hair loss by patient report (VAS) at follow-up (FUP). Tolerability and satisfaction were assessed by patient report.
Results 103 patients enrolled between 7/2010 and 6/2015; 97 are evaluable for the primary endpoint. Chemotherapy included docetaxel/cyclophosphamide (TC; $n = 50$) for 4–6 cycles every 3 weeks, weekly paclitaxel for 12 weeks then doxorubicin/cyclophosphamide (P/AC; $n = 23$) for 4 cycles every 2–3 weeks, AC then paclitaxel (AC/P; $n = 10$), docetaxel/carboplatin ± trastuzumab (TCH; $n = 4$) for 4–6 cycles every 3 weeks. Overall, 61% of patients successfully prevented CIA; impact was regimen specific: TCH 100%, TC × 4 84%, TC × 5–6 50%, P/AC 43%, AC/P 20%. The most common toxicity was headache, reported by 78.5% of patients with mean pain level 37/100. Satisfaction among those who completed scalp cooling (SC) and FUP ranged from 74 to 100%. All patients who completed SC/FUP recommended Penguin.
Conclusions Scalp hypothermia with Penguin is effective in reducing alopecia, particularly for non-anthracycline-based shorter regimens. Penguin was well tolerated and viewed favorably by most patients.

Keywords Breast cancer · Alopecia · Chemotherapy · Scalp cooling

Abbreviations list

AC	Doxorubicin/cyclophosphamide
CIA	Chemotherapy-induced alopecia
FDA	Food and Drug Administration
FUP	Follow-up
P	Paclitaxel
PCC	Penguin Cold Cap
PSC	Paxman scalp cooling
SC	Scalp cooling
TC	Docetaxel/cyclophosphamide
TCH	Docetaxel/carboplatin/trastuzumab
UCSF	University of California, San Francisco
VAS	Visual Analog Scale

Background

Recent medical advances have helped to mitigate many chemotherapy-related side effects. However, chemotherapy-induced alopecia (CIA) remains a distressing side effect of chemotherapy treatment. Some of the most effective and commonly administered chemotherapy regimens for breast cancer, including anthracyclines and taxanes, cause complete alopecia [1]. This toxicity is mostly

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but not always reversible [2], and hair can take a year or more to regrow. CIA has been shown to affect female breast cancer patients who report loss of self-confidence and increased concern over being publicly identified as a cancer patient [3]. Complete alopecia is a reminder to the patient and others of her disease, and patients have reported negative effects on self-image, quality of life, and normal social and professional functioning [4]. In an effort to better manage side effects and improve quality of life while on chemotherapy, interventions for CIA have gained attention.

Since the 1970s, the primary method of reducing CIA has been through the use of scalp-cooling devices. Scalp cooling is thought to prevent hair loss via vasoconstriction, decreasing the amount of chemotherapy delivered to the scalp and reducing the cellular uptake of drugs and intrafollicular metabolic rate [5, 6]. Although the overall efficacy of scalp cooling remains inconclusive and variable, recent studies have reported success using this intervention method for CIA.

The University of California San Francisco (UCSF) Penguin Cold Cap Registry study was initiated in 2010 as part of an overall program to objectively evaluate scalp-cooling devices (Hair to Stay Program). The primary aims were evaluated using patient-reported tolerability as well as patient and clinician assessments of the efficacy of scalp hypothermia using the Penguin Cold Cap System in women undergoing chemotherapy for early or advanced stage breast cancer.

Methods

Cap cooling and storage freezers were purchased and made available for routine use at the UCSF Breast Care Center using philanthropic donation to the Hair to Stay Program. Patients scheduled to receive a chemotherapy regimen with anticipated alopecia who expressed interest in hair preservation were provided general information regarding access to caps through the Penguin Cold Caps distributor and were offered the opportunity to participate in the registry. The registry study was approved by the UCSF Committee on Human Research with the understanding that the device was not FDA approved and patients had decided to use the Penguin Cold Caps independent of study participation. Written informed consent was obtained from all individual participants in the registry study. Patients were not provided any financial support to rent the caps and did not receive specific information or guidance on the use of the Penguin Cold Caps from staff at UCSF.

Hair loss was separately assessed by both patient and provider at baseline, every 3–4 weeks during chemotherapy, and at least 1 month after completion of chemotherapy. Patients used 100-point Visual Analog Scales (VAS) to report their own hair loss (0 = no hair loss; 100 = complete hair loss) and their satisfaction with their hair (0 = completely dissatisfied; 100 = completely satisfied). Providers evaluated hair loss using a 5-point Dean scale (0 = no hair loss; 1 = up to 25%; 2 = 26–50%; 3 = 51–75%; 4 = 76% or more). Treatment success was defined as completion of scalp cooling with $\leq$50% hair loss at all time points by patient report. Patients who discontinued scalp cooling due to hair loss or scalp-cooling-related toxicity were documented as treatment failures, including documentation of whether it was because of intolerability or lack of efficacy. For the efficacy endpoint, evaluable patients were defined as those who completed scalp cooling or discontinued scalp cooling due to hair loss or device-related side effects. We did not include patients who were lost to follow-up or who discontinued chemotherapy due to toxicities unrelated to scalp cooling.

We calculated the mean maximum VAS and mean maximum Dean score by chemotherapy regimen using the maximum scores ever reported for each patient throughout scalp cooling and follow-up. Patients who discontinued scalp cooling due to hair loss were assigned the maximum VAS score of 100 and maximum Dean score of 4. Patients who discontinued due to scalp-cooling-related toxicity were not included in these calculations.

To assess tolerability, patients recorded the magnitude of headache, sensation of feeling chilled, and scalp pain on 100-point VAS scales, and described any other side effects. At follow-up, patients who completed chemotherapy and scalp cooling were asked to rate their satisfaction with the Penguin Cold Caps system on a 5-point Likert scale (very dissatisfied—dissatisfied—neither satisfied nor dissatisfied—satisfied—very satisfied) and indicate whether they would recommend the system to another patient receiving the same chemotherapy regimen (would not recommend—recommend to some degree—highly recommend).

Results

103 patients enrolled in the registry between July 2010 and June 2015. Table 1 summarizes demographic information for all patients enrolled. 97 patients are evaluable for the primary endpoint; 3 dropped out due to stopping chemotherapy; 3 were lost to follow-up or had incomplete efficacy data from both patient and physician report. Mean time to follow-up reporting after completing chemotherapy was 17 weeks. Of evaluable patients, 15/97 (15.5%) prematurely discontinued scalp cooling: 9/97 (9.3%) due to hair loss and 6/97 (6.2%) due to device-related side effects. The chemotherapy regimens for the remaining 82 patients

Table 1 Patient demographics

Patient characteristic	
Age (median)	48.3 (range 27.1–83.1) (mean 49.1, SD = 10.7)
Menopausal status	
Pre-menopausal	64 (62%)
Post-menopausal	39 (38%)
Ethnicity[a]	
White	79 (77%)
Black	3 (3%)
Hispanic	7 (7%)
Asian	14 (14%)
Middle Eastern	3 (3%)
Chemotherapy setting	
Neoadjuvant	30 (29%)
Adjuvant	60 (58%)
Metastatic	13 (13%)

[a]Total percentage is >100 because some patients reported multiple ethnicities

and the distribution of those who discontinued scalp cooling are shown in Table 2. According to patient self-assessment, 59/97 (60.8%) evaluable registry participants successfully prevented alopecia, with the most successful results reported for those receiving 4 cycles of docetaxel-cyclophosphamide (83.8%, 31/37 pts) or docetaxel-carboplatin with or without trastuzumab (100%, but only 2 patients evaluable). The overall mean maximum VAS hair loss reported by patients was 47. Rates of successful alopecia prevention and mean maximum VAS by chemotherapy regimen are shown in Table 3. Of patients who completed follow-up, the majority reported that they were either 'satisfied' (21.5%) or 'very satisfied' (67.1%) with how well the Penguin Cold Cap system worked to prevent hair loss. In fact, 100% reported that they would recommend the system to another patient receiving the same chemotherapy regimen. Patient satisfaction and recommendation rates are summarized in Table 4.

Tolerability

6/97 evaluable patients (6.18%) discontinued scalp cooling due to device-related side effects. Of these, four patients discontinued scalp cooling during their first session and provided no survey data regarding device-related side effects. Of the remaining 93 pts, 73/93 (78.5%) experienced headaches at least once and 55/93 (59.1%) reported headaches at least half of the time during cap use, with a mean headache VAS score of 36.9 (SD = 20.3). When asked to report the amount of chill and scalp pain experienced during each scalp-cooling session, patients reported a mean chill VAS score of 49.8 (SD = 23.6) and a mean scalp pain VAS of 32.7 (SD = 23). The other most commonly reported side effects were nausea (24.7%, 23/93) and scalp itchiness or dandruff (19.4%, 18/93).

Discussion

Our registry study represents one of the largest series of patients undergoing scalp cooling using Penguin Cold Caps with chemotherapy regimens commonly utilized in the United States, including both anthracyclines and taxanes. These data suggest that scalp cooling with Penguin Cold Caps is an effective and tolerable option for many women receiving chemotherapy treatment for breast cancer, but efficacy remains dependent on chemotherapy regimen. Scalp cooling was highly effective for patients receiving four cycles of docetaxel-cyclophosphamide (TC), with most women successfully preventing CIA (83.8% by patient report; 80% by physician report). These results support the 90% success rate by Cigler et al. for a cohort of 20 breast cancer patients who also used the Penguin Cold Cap with TC × 4 [7]. Similarly, Rugo et al. documented

Table 2 Chemotherapies received by patients enrolled

Chemotherapy regimen	Pts enrolled in registry	Discontinued scalp cooling			Lost to follow-up (%)
		Due to device-related side effects (%)	Due to hair loss (%)	Discontinued chemotherapy for toxicity unrelated to scalp cooling (%)	
TC × 4	40	0	2 (5)	3 (7.5)	0
TC × 5–6	10	1 (10)	0	0	0
P/AC	23	1 (4.3)	2 (8.7)	0	0
AC/P	10	2 (20)	2 (20)	0	0
T/Carboplatin × 4–6 (±Herceptin)	4	0	0	0	2 (50)
Other	16	2 (12.5)	3 (18.75)	0	1 (6.25)
Overall	103	6 (5.8)	9 (8.7)	3 (2.9)	3 (2.9)

TC docetaxel/cyclophosphamide, *P* paclitaxel, *AC* doxorubicin/cyclophosphamide

Table 3 Chemotherapy regimens

Chemotherapy regimen	Evaluable pts	Successful alopecia prevention		Mean maximum VAS by pt report
		% success by patient self-assessment (≤50% hair loss)	% success by physician report (Dean's score ≤2)	
TC × 4	37	83.8% (31)	80% (28/35[a])	38.6
TC × 5–6	10	50% (5)	75% (6/8[a])	44.4
P/AC	23	43.4% (10)	55.5% (10/18[a])	58.9
AC/P	10	20% (2)	20% (2/10)	62.5
T/Carboplatin × 4–6 (±Herceptin)	2	100% (2/2)	100 (1/1[a])	20
Other	15	60% (9)	61.5% (8/13[a])	46.9
Overall	97	60.8% (59)	64.7% (55/85[a])	47

[a]Data unavailable for remaining patients

Table 4 Patient satisfaction

Chemotherapy regimen	Pts completed scalp cooling and follow-up	% Satisfied with Penguin Cold Cap (*n*)	% recommending Penguin Cold Cap (*n*)
TC × 4	35	94 (32/34[a]) Satisfied = 20.6 (7/34) Very satisfied = 73.5 (25/34)	100 (35)
TC × 5–6	9	87.5 (7/8[a]) Satisfied = 50 (4/8) Very satisfied = 37.5 (3/8)	100 (9)
P/AC	20	73.7 (14/19[a]) Satisfied = 26.3 (5/19) Very satisfied = 47.4 (4/19)	100 (20)
AC/P	6	100 (6) Satisfied = 16.7 (1) Very satisfied = 8.3 (5)	100 (6)
T/Carboplatin × 4–6 (±Herceptin)	2	100 (2) Very satisfied = 100 (2)	100 (2)
Other	10	90 (9) Very satisfied = 90 (9)	100 (10)
Overall	82	88.6 (70/79[a]) Satisfied = 21.5 (17/79) Very satisfied = 67.1 (53/79)	100 (82)

[a]Data unavailable for remaining patients

successful (defined as ≤50% hair loss) CIA prevention in 60.5% of patients (patient self-assessed) with TC × 4 [8], results that recently led to FDA clearance of the DigniCap device. Using the Paxman system, the SCALP randomized clinical trial reported successful hair preservation in 50.5% (48/95) of women; specific chemotherapy regimens were not provided [9]. Thus, our findings are consistent with recent studies exploring scalp-cooling devices to address CIA as an unmet need for breast cancer patients, and have suggested that scalp cooling may be particularly successful for women receiving the chemotherapy regimen consisting of TC × 4.

Interestingly, almost half of patients receiving P/AC successfully prevented CIA (43.4% by patient report; 55.5% by physician report), but there was a wide variability in amount of total hair loss with maximum VAS scores ranging from 5 to 100. Earlier studies have reported mixed results using various scalp-cooling systems for patients treated with anthracycline and taxane combination therapies [10]. For example, the Dutch Scalp Cooling Registry, which defined successful hair preservation by "lack of use of head covering," documented "success" in only 8% of 66 patients who used the Paxman PSC1 or PSC2 cooling system with TAC (docetaxel, doxorubicin,

and cyclophosphamide) [11]. However, they also documented a 39% (29/74) success rate with 4 cycles of AC, a 48% (14/29) success rate for AC followed by weekly paclitaxel, and a 29% (6/21) success rate with AC × 4 cycles followed by paclitaxel at 175 mg/m2 for 4 cycles. Schaffrin-Nabe et al. reported "no scalp cooling success" for patients using the DigniCap system with TAC or epirubicin (≥100 mg/m^2) and cyclophosphamide followed by paclitaxel [12].

Notably, we observed a 20% lower success rate reported by both patient and physician for patients who received anthracycline before paclitaxel (AC/P), compared to patients who received paclitaxel before anthracycline (P/AC). However, it should be noted that two patients who successfully prevented CIA with AC/P reported very little hair loss, with maximum VAS scores of ≤10. Thus, the difference in efficacy for patients receiving the same chemotherapy drugs but in a different sequence is intriguing and deserves further investigation. The finding that patients had greater scalp-cooling success when weekly paclitaxel was administered prior to the start of an anthracycline may impact future selection of chemotherapy regimens, if an anthracycline-based regimen is being considered, especially when order of therapy does not matter.

One unique aspect of our study was the high acceptability and favorability of the Penguin Cold Caps based on patient satisfaction ratings. All patients who completed scalp cooling—even those who were considered treatment failures—reported that they would either highly recommend or recommend to some degree use of the Penguin Cold Cap to another patient receiving the same chemotherapy regimen. Although this finding did not include patients who discontinued scalp cooling due to device-related side effects (6%) or due to hair loss (8%), we suspect that this result may serve as a proxy for patient quality of life during active cancer treatment. Recent findings from Rugo et al. found that women with successful hair preservation (Dean score of 0 to ≤2) were less likely to agree with the question, "Have you felt physically less attractive as a result of your disease or treatment?", than women with Dean scores of 3 or 4 (18.5 vs. 52.2%; $p < 0.002$), suggesting that prevention of CIA using scalp cooling is associated with higher quality of life [8]. Our findings suggest that the mere act of scalp cooling (i.e., participating in an activity that permits some degree of patient self-efficacy) may have a positive impact on patient quality of life. Future research should incorporate more explicit quality of life assessments to improve understanding of what drives positive patient recommendation of Penguin Cold Caps despite variable and somewhat unpredictable scalp-cooling efficacy.

Another unique aspect of our registry study is the inclusion of 12 patients with metastatic disease who sought the use of scalp cooling for a variety of regimens including eribulin mesylate and weekly nab-paclitaxel. Pts used the caps for an average of 3 months. Six discontinued the caps due to change of treatment, two due to side effects, two due to hair loss, and two were lost to FUP (one passed away before FUP, one lost contact). One of the two patients who dropped out due to hair loss used the caps for 5 months before dropping out. The patient who passed away before FUP used the caps for 2.6 months and reported a maximum hair loss of 20%, suggesting benefit during the time she used the caps. Interestingly, one author (MM) has observed in her practice that some patients in the metastatic setting are strongly influenced by hair loss and decline or delay accepting chemotherapy regimens strongly associated with CIA in lieu of potentially less effective treatment options. The possibility of scalp cooling in the metastatic setting—especially for patients who need to initiate chemotherapy for only a short period of time—may be an appealing option to patients with metastatic disease, many of whom express the desire not to die "bald."

Although our data suggest high efficacy and tolerability of the Penguin Cold Caps for scalp cooling, potential limitations should also be mentioned. First, research has suggested that excessive use of chemical dyes, parabens, and heat can weaken or damage hair follicles [13]. Because we did not assess at-home hair-care regimens, we cannot evaluate the impact such procedures may have had on the effectiveness of scalp cooling. Second, we did not examine potential moderators including high motivation and proactive behavior that may have distinguished our self-selected patient sample from a larger and more diverse population. Third, self-report assessments have the potential to contain cognitive bias and can vary with different contexts [14]. Although physician report of hair loss helped to counteract any bias in self-report, incorporation of an independent assessment of hair loss by a party blinded to the patient's chemotherapy regimen may be preferable. As popularity of scalp-cooling devices increases, future research should include a standardized protocol including instruction on hair-care and maintenance as well as comprehensive patient questionnaires and/or diaries designed to increase effectiveness and generalizability of scalp-cooling procedures. Finally, despite increased patient and advocate interest in scalp cooling for prevention of CIA, many oncologists remain concerned about the potential risk of scalp metastasis. Although no study to date has demonstrated a statistically significant increase in scalp metastasis for patients undergoing scalp cooling [15], our registry did not specifically track the occurrence of scalp metastasis in our patients via long-term follow-up.

With increased awareness and availability of safety and efficacy data as well as the recent FDA clearance of the DigniCap device, scalp cooling will likely become a more

widely available supportive care option in the United States. While access to the DigniCap or Paxman devices may remain limited (i.e., not available in many community oncology offices), the Penguin Cold Caps, which can be rented and used by patients at any treatment facility, offer a reasonable option for patients hoping to prevent CIA. Although concern regarding the cost of Penguin Cold Caps or other device rental—which may range from $1500 to $3000 or more—remains, national and local organizations such as Hair to Stay [16] continue to grow and fundraise to provide patient subsidies, often making scalp cooling more accessible for lower income patients. Further research on scalp-cooling devices such as the Penguin Cold Caps is necessary to optimize efficacy of the device and evaluate its impact on treatment decision-making and patient quality of life, as well as to positively promote insurance coverage for scalp cooling as a meaningful aspect of cancer supportive care. The side effect of hair loss is of great concern and importance to our patients and should be prioritized in our research agenda, especially for the recovery and well-being of our patients.

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Compliance with ethical standards:

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All research involved in this investigation complied with the appropriate United States laws. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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