

Efficacy of scalp cooling in reducing alopecia in early breast cancer patients receiving contemporary chemotherapy regimens

Arlene Chan ^{a,*}, Astrid Bauwens ^b, Sally Pontre ^c, Sally Jackson ^c, Frances McGlone ^c,
Tracie Ernenwein ^c, Jun Chih ^d, Christopher Reid ^d

^a Breast Cancer Research Centre-WA and Curtin University, Perth, WA, Australia

^b Ramsay Health, Perth, WA, Australia

^c Breast Cancer Research Centre-WA, Nedlands, WA, Australia

^d Schools of Public Health & Preventative Medicine, Curtin University & Monash University, Australia

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ABSTRACT

Introduction: Hair loss as a result of chemotherapy for early breast cancer (EBC) is a frequent and distressing side effect. Minimising hair loss may improve mood and body image. Our aim was to determine scalp cooling (SC) efficacy in EBC patients receiving contemporary chemotherapy regimen, to inform future patients choice to use SC or not.

Methods and Results: Prospective cohort study of 60 stage 1–3 EBC patients recommended to receive taxane or anthracycline-taxane chemotherapy regimens. The primary outcome was incidence of minimal hair-loss (MHL - defined as 60% Dean grade 1 or 2). Patients were categorised by chemotherapy (3 groups) and randomised 1:1 within each group to two scalp cooling temperature settings using the Dignitana Dignicap machine (secondary endpoint). Patients reported degree of hair loss using the Dean score on day 1 of each cycle and following the last chemotherapy.

Results: On an intention-to-treat basis, 33% of patients reported MHL, thus our primary endpoint was not achieved. Patients receiving taxane-only chemotherapy had the highest rate of MHL (45%). No other factors (including hair type, age, body weight, temperature setting) predicted for MHL. Patient-reported anxiety reduced significantly in all patients, but no difference was observed for depression or body image irrespective of degree of hair loss. SC-related adverse events were uniformly of low grade and all resolved.

We would recommend the use of SC for all patients receiving taxane-based chemotherapy, with its use for those patients recommended for anthracycline-taxane regimens being made on an individual basis. Trial Registration anztr.org.au ACTRN12615001106527.

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1. Introduction

Chemotherapy-induced alopecia (CIA) is one of the most commonly occurring and distressing side effect of breast cancer treatment. Studies indicate that even with the knowledge of temporary hair loss, more than half of respondents describe this symptom as being burdensome, as well as an outward sign of cancer associated with negative self-image and feelings of depression and anxiety [1–5].

Although CIA is almost always reversible after chemotherapy, current options to prevent CIA from occurring are limited [1,3]. Scalp cooling (SC) to reduce the degree of CIA has been utilised for over 40 years and is currently the most effective technique in reducing CIA when compared with no scalp cooling [3,6–8].

Despite consensus in the literature that scalp cooling is effective, several variables have been suggested to influence its success. These include hair thickness, type and dose of chemotherapy treatment, scalp temperature and cap fitting technique [9]. Scalp cooling in patients receiving taxane-based regimens has been shown to be more effective than those receiving anthracycline with or without taxanes [1,6]. It has been suggested that lowering the scalp subcutaneous tissue to 22 °C is necessary to prevent alopecia, with pre-clinical studies, suggesting that temperatures of

* Corresponding author. Breast Cancer Research Centre-WA, 101 Monash Ave, Nedlands, Perth, WA 6009, Australia.

E-mail address: arlenechan@me.com (A. Chan).

14 °C–18 °C may be even more effective [9,10].

This study was initiated in an effort to address the comparative efficacy of SC in women receiving different contemporary chemotherapy regimens, in an effort to inform future patients in their decision-making as to whether to use SC or not. Further we explored the impact of the degree of CIA on mood and body image, whether lowering the SC temperature beyond the usual setting of 5 °C could lead to greater efficacy and plan long-term follow-up to observe for the incidence of scalp metastases.

2. Materials and methods

2.1. Study design

Consecutive patients with stage I to III breast cancer treated in a single institution were invited to participate in this study. The key inclusion criteria included women aged over 18 years who were recommended to receive one of the following chemotherapy regimens docetaxel cyclophosphamide (TC), docetaxel, cyclophosphamide and trastuzumab (TCH), docetaxel, doxorubicin, cyclophosphamide (TAC), doxorubicin, cyclophosphamide (AC), doxorubicin, cyclophosphamide – paclitaxel (AC-P) (2 or 3 weekly), fluorouracil, epirubicin and cyclophosphamide – docetaxel (FEC-D) in the neoadjuvant or adjuvant setting; conversant in English; provided signed consent and agreed to undergo follow-up for 10 years. Patients were ineligible if chemotherapy was given on a weekly schedule; had a history of cold sensitivity, cold agglutinin disease, cryoglobulinemia, cryofibrinogenemia or cold traumatic dystrophy; had existing alopecia of any grade as assessed by the clinician and were known to have hypersensitivity to silicon.

Consenting patients were categorised according to their recommended treatment regimen as determined by the treating oncologist: Cohort 1 taxane-based regimens - TC or TCH; Cohort 2 concurrent anthracycline and taxane - TAC and Cohort 3 anthracycline with or without sequential taxane – AC, AC-P, FEC-D (Fig. 1).

Cohort 1 underwent treatment TC (docetaxel 75 mg/m², cyclophosphamide 600 mg/m²); TCH (docetaxel 75 mg/m², carboplatin AUC 6, trastuzumab 8 mg/kg loading and 6 mg/kg every 21 days for 52 weeks), Cohort 2 underwent treatment TAC (docetaxel 75 mg/m², doxorubicin 60 mg/m², cyclophosphamide 600 mg/m²), Cohort 3 underwent treatment FEC-D (fluorouracil 500 mg/m², epirubicin 100 mg/m², cyclophosphamide 500 mg/m², docetaxel 100mg/m², AC-P (doxorubicin 60 mg/m², cyclophosphamide 600 mg/m², paclitaxel 175 mg/m²).

Patients within each cohort were randomised on a 1:1 ratio to

the SC system set at 5 °C or 3 °C for the duration of their chemotherapy treatment. This was done by a member of staff uninvolved in the trial conduct and using a sequentially numbered card system. The treating clinician were blinded to the temperature assignment.

The primary outcome measure was to assess the proportion of patients who self-reported Dean score grade 1 or 2 (<25% and 25%–50% hair loss, respectively and defined as minimal hair loss) at two to four weeks after completion of chemotherapy compared to baseline. Secondary outcome measures included association of hair loss to anxiety, depression and body image; an exploratory evaluation of the efficacy between temperature setting of 3 °C as compared to 5 °C. The default temperature setting of 5 °C is considered to be equivalent to a scalp temperature of 22 °C. We hypothesized lowering the temperature setting on this system to 3 °C would simulate a scalp temperature below 22 °C. All SC-related adverse events were reported from commencement of chemotherapy until up to 28 days following the last cycle. The study received ethics approval from the institutional human ethics and research committee and was conducted in accordance with the Helsinki Declaration.

2.2. Treatment

The Dignitana Dignicap is a TGA approved refrigerated cooling system – the details of machine schematics are well documented. Prior to the first cycle of chemotherapy, the appropriate sized cap for each patient was determined by the study nurse. At the start of each treatment, the patient's cap was fitted by the study nurse in accordance with the product information recommendations and the temperature was set according to assigned randomisation. SC was initiated 30 min prior to the start of chemotherapy with the cooling cap worn throughout chemotherapy treatment and for a further 90 min following chemotherapy completion.

2.3. Study assessments

Patients reported degree of hair loss using the 5-point Dean's scale [11], as did the treating clinician, on day one from cycle two onwards (comparing this to the cycle immediately preceding) and then at 14–28 days after the last cycle of (comparing this to baseline). All other study assessments were done at this same time point throughout the study. Patient mood was assessed by the Patient Health Questionnaire-9 (PHQ-9) [12] and Generalised Anxiety Disorder (GAD-7) [13], whilst the patient's body image was assessed with the Body Image Scale (BIS) [14] questionnaires. Information on the use of any head covering was also collected. An optional consent was signed by patients who were agreeable for a pre- and post-chemotherapy photograph of their hair. Patients who utilised the SC for all cycles of chemotherapy were asked at the end of chemotherapy treatment if they considered the device worthwhile and whether they would use SC again, if needed in the future. Adverse events were recorded throughout the study and assessed by the investigator as to a causality relationship to the SC device.

2.4. Statistical analyses

For the primary outcome, we anticipated that the incidence of patients reporting minimal hair loss (i.e. Dean score of 1 or 2) after completion of planned cycles of chemotherapy would be 60% in the population overall, as compared to the 5% or lower incidence traditionally seen in this clinical setting without the use of SC. To detect this difference with 80% power at a one-sided significant level of 0.025 (lower from 0.05 as Bonferroni correction applied to enable multiple groups comparisons), stratifying for treatment cohorts, a final sample of 10 per group was required. Assuming a

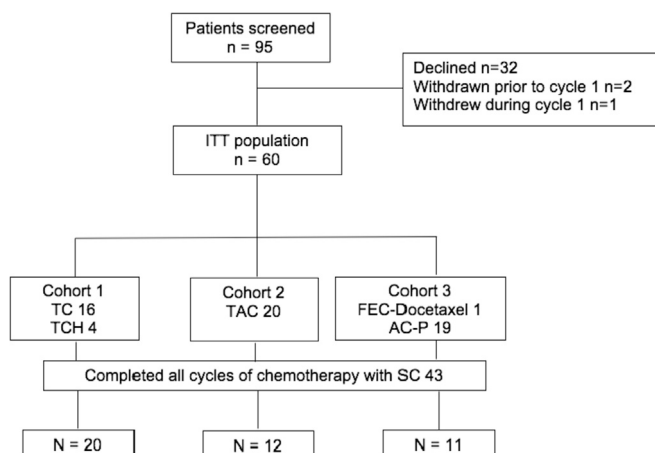


Fig. 1. CONSORT diagram.

50% dropout rate, 20 patients were recruited for each chemotherapy group.

Descriptive statistics of patient characteristics were reported as mean and standard deviation (or median and range if the variable is skewed) or frequency and percentages. The rates of adherence with the use of SC for all planned number of chemotherapy cycles were calculated. Differences between baseline and post-treatment score of patient mood and body image were analysed using paired-samples *t*-test. The impact of hair loss on mood and body image score after the treatment were analysed using logistic regression while adjusting for the baseline scores. Significance level was set at 5%. All analyses were done using Stata 14 (StataCorp LP). A weighted kappa score was used to assess for the degree of agreement between the patient's reporting of the degree of hair loss with that of the clinician.

3. Results

3.1. Patients characteristics

From December 2015 to February 2017 a total of 95 eligible patients were offered entry to the study. One-third (32) of eligible patients declined, with reasons including hair loss being unimportant, concerns regarding discomfort from wearing the device

and the inconvenience of additional time required to receive treatment. Three patients were excluded from the analysis (2 withdrew consent before commencing chemotherapy, 1 ceased SC during cycle 1); thus, the intent to treat (ITT) population comprised of 60 patients who were evaluable for the primary endpoint and safety. The median age was 48 years (range, 25–86) with 63% of patients being premenopausal or perimenopausal. There was one Asian patient with all other patients being Caucasians. Overall, there was moderate to severe anxiety and/or depression reported in 25% and 4% of patients, respectively (Table 1).

3.2. Primary and secondary endpoints

For the ITT population, 33% of patients reported minimal hair loss with this proportion increasing to 40% if limited to the 43 patients who used the SC for the total duration of their chemotherapy (Table 1). The treatment group with the highest rate of minimal hair loss were those patients receiving taxane-only chemotherapy (45%), with those receiving concurrent anthracycline-taxane having the lowest rate (20%). Examples of patients reporting minimal hair loss from each cohort are shown in Fig. 2.

There was 100% compliance with SC for all cycles of chemotherapy in patients receiving non-anthracycline regimens, whilst

Table 1
Patient characteristics (n=60).

Variables	Overall (n = 60)	^a Cohort 1 (n = 20)	Cohort 2 (n = 20)	Cohort 3 (n = 20)
n (% within cohort)				
Age years, median	48	49.5	45.1	54.9
range	25–86	40–72	25–53	34–86
Pre- or Perimenopausal	38 (63)	9 (45)	20 (100)	9 (45)
Postmenopausal	22 (37)	11 (55)	0	11 (55)
Use of head covering^b				
No	12 (21)	8 (40)	1 (6)	3 (17)
Yes	44 (79)	12 (60)	17 (94)	15 (83)
BMI kg/m ² (mean ± sd)	25.9 ± 5.5	25.4 ± 4.5	24.6 ± 3.3	27.6 ± 7.6
GAD baseline (%)				
Minimal 0–4	24 (40)	7 (35)	8 (40)	9 (45)
Mild 5–9	21 (35)	9 (45)	6 (30)	6 (30)
Moderate 10–14	9 (15)	2 (10)	6 (30)	1 (5)
Severe 15–21	6 (10)	2 (10)	0	4 (20)
PHQ baseline (%)				
Minimal 1–4	36 (60)	14 (70)	11 (55)	11 (55)
Mild 5–9	16 (27)	4 (20)	7 (35)	5 (25)
Moderate 10–14	6 (10)	2 (10)	2 (10)	2 (10)
Mod severe 15–19	1 (2)	0	0	1 (5)
Severe 20–27	1 (2)	0	0	1 (5)
GAD end (%)				
Minimal 0–4	43 (77)	16 (80)	14 (78)	13 (72)
Mild 5–9	10 (18)	4 (20)	3 (17)	3 (17)
Moderate 10–14	3 (5)	0	1 (5)	2 (11)
Severe 15–21	0	0	0	0
PHQ end (%)				
Minimal 1–4	6 (64)	17 (85)	10 (56)	9 (50)
Mild 5–9	14 (25)	3 (15)	6 (33)	5 (28)
Moderate 10–14	3 (5)	0	1 (5)	2 (11)
Mod severe 15–19	3 (5)	0	1 (5)	2 (11)
Severe 20–27	0	0	0	0
Hair loss (ITT)^c				
Minimal	20 (33)	9 (45)	4 (20)	7 (35)
Severe	40 (67)	11 (55)	16 (80)	13 (65)
Hair loss (SC used for all cycles, n=43)^c				
Minimal	17 (40)	9 (45)	3 (25)	5 (46)
Severe	26 (60)	11 (55)	9 (75)	6 (54)

^a Cohort 1 underwent treatment TC (docetaxel 75 mg/m², cyclophosphamide 600 mg/m²); TCH (docetaxel 75 mg/m², carboplatin AUC 6, trastuzumab 8 mg/kg loading and 6 mg/kg every 21 days for 52 weeks); Cohort 2 underwent treatment TAC (docetaxel 75 mg/m², doxorubicin 60 mg/m², cyclophosphamide 600 mg/m²), Cohort 3 underwent treatment FEC-D (fluorouracil 500 mg/m², epirubicin 100 mg/m², cyclophosphamide 500 mg/m² followed by docetaxel 100 mg/m²; AC-P (doxorubicin 60 mg/m², cyclophosphamide 600 mg/m², paclitaxel 175 mg/m²).

^b Missing data.

^c Dean score at time of end of trial.



Fig. 2. Patients who reported minimal hair loss.

40%–45% of patients ceased SC in cohort 2 and 3, respectively (Table 1).

The degree of hair loss as reported by the patient at each visit was compared to that made by the clinician. Paired assessments were available for the clinician and patient on 330 of 352 visits where the weighted kappa score for agreement was 0.205, which equates with fair strength in agreement. There was a tendency for the clinician to rate the degree of hair loss at a lower grade than that reported by the patient.

At baseline, the majority of patients reported minimal to moderate anxiety (median GAD-7 of 5) with 10% of patients reporting severe anxiety. Similarly, most patients (96%) reported minimal to moderate depression (median PHQ of 3). In regard to body image, the median score was 4 at baseline, but with 20% of patients reporting having a poor body image (data not shown). Patient assessment following completion of chemotherapy showed that among those who reported minimal hair loss, a significant improvement was seen in patient reported levels of anxiety with a decline in mean GAD-7 score of 5.9 to 3.2 ($p = 0.002$, Fig. 3).

In the group overall there was no significant difference seen for depression and body image (Table 2).

There was a trend towards worse body image in the group of patients who experienced severe hair loss with a mean BIS of 3.9 at baseline increasing to 5.6 at the end of chemotherapy ($p = 0.06$). However, when the impact of hair loss was evaluated after adjusted for treatment group and baseline scores, there was no significance seen in anxiety, depression and body image score post treatment (data not shown).

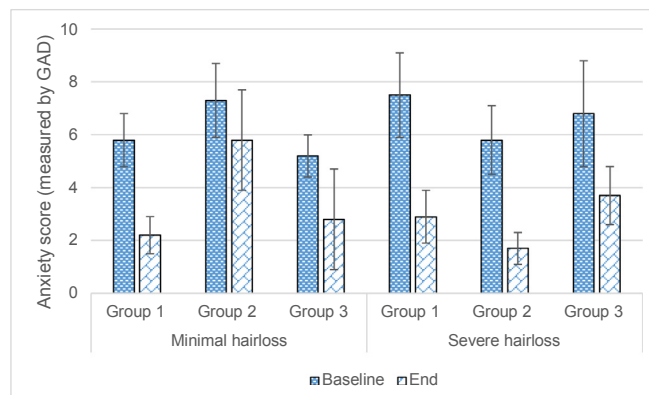


Fig. 3. Anxiety score (mean $\pm$ SE) reported by patients of 3 treatment groups by minimal and severe hair loss.

Head covering was never worn throughout chemotherapy in 13 patients (22%) but this was not associated with the degree of hair loss. Seven patients (35%) with minimal hair loss and six patients (15%) with severe hair loss chose not use head covering. Conversely, 85% of patients experiencing severe hair loss by end of chemotherapy had reported using head covering for 2 to >5 times each week as compared to 65% of those who had reported minimal hair loss. In particular, all patients in cohort 2 reported use of hair covering at some time during chemotherapy.

There was no difference in rates of minimal hair loss reported whether patients received SC at a temperature setting of 3 °C or 5 °C, in both the ITT or population who utilised SC for all chemotherapy cycles (data not shown).

All patients completed the planned number of cycles of chemotherapy irrespective of withdrawal from using SC or not. Seventeen patients (28%) ceased SC prior to the end of their chemotherapy and reasons given for withdrawal were an adverse event (headache 2, 12%), lack of efficacy (5, 29%) and the inconvenience of prolongation of chemotherapy treatment time (10, 59%).

At the end of study visit, the 43 patients who completed all chemotherapy using SC were asked as to their satisfaction with the use of SC and whether they would make use of the device again, were it ever to be required. Irrespective of the degree of hair loss, 81% and 72% of patients stated they were very satisfied with the device and would consider using it again, respectively. All patients who stated that they were dissatisfied with the SC had experienced severe hair loss (8 patients) and five of these eight patients stated they would not utilise the SC if offered again.

3.3. Adverse events

In the ITT population, 106 adverse events occurred with 66 events (in 33 patients) considered likely or possibly to relate to the use of SC. The vast majority (92%) were grade 1 events including mild scalp pain, headache, dizziness, dry skin, itchy skin and rash, with all symptoms resolving after a median duration of 2 days (1–66). Four patients complained of grade 2 headache which resolved in less than 4 days and 1 patient had grade 3 headache which resolved with analgesia following 5 days. Two patient experiencing grade 1 headache cited this as the reason for withdrawal from the trial.

4. Discussion

Alopecia resulting from chemotherapy in women with breast cancer has been ranked in the top five most distressing side effects

Table 2
Mean scores (standard error) of general anxiety, patient health and body image at baseline and end of study of patients with minimal and severe hair loss, by treatment group.

	Minimal hair loss				Severe hair loss			
	Overall (n = 19)	Group 1 (n = 9)	Group 2 (n = 4)	Group 3 (n = 6)	Overall (n = 37)	Group 1 (n = 11)	Group 2 (n = 14)	Group 3 (n = 12)
GAD-7								
Baseline	5.9 (0.6)	5.8 (1.0)	7.3 (1.4)	5.2 (0.8)	6.6 (0.9)	7.5 (1.6)	5.8 (1.3)	6.8 (2.0)
End	3.2 (0.8)	2.2 (0.7)	5.8 (1.9)	2.8 (1.9)	2.7 (0.5)	2.9 (1.0)	1.7 (0.6)	3.7 (1.1)
95% CI of mean difference	(1.2, 4.3)	(2.0, 5.1)	(-2.3, 5.3)	(-2.9, 7.6)	(2.2, 5.6)	(1.1, 8.0)	(0.7, 7.5)	(0.1, 6.2)
p-value	0.0017	0.007	0.2967	0.3053	0.001	0.0153	0.0221	0.0439
PHQ-9								
Baseline	3.9 (0.6)	3.4 (0.6)	5.5 (1.6)	3.5 (1.0)	4.7 (0.7)	4.2 (1.3)	4.5 (0.9)	5.3 (1.7)
End	4.3 (1.0)	2.9 (0.6)	7 (3.1)	4.5 (2.4)	4.3 (0.5)	2.8 (0.7)	4 (0.7)	5.9 (1.2)
95% CI of mean difference	(-2.2, 1.5)	(-1.3, 2.4)	(-9.3, 6.3)	(-6.3, 4.3)	(-0.9, 1.7)	(-0.9, 3.7)	(-1.7, 2.7)	(-3.2, 2.1)
p-value	0.6790	0.5077	0.5860	0.6488	0.5161	0.2147	0.6250	0.6354
BIS								
Baseline	6.1 (1.1)	4.8 (1.3)	10 (3.1)	5.3 (2.1)	3.9 (0.7)	5.3 (2.0)	3.2 (0.8)	3.3 (1.0)
End	6.2 (1.4)	5.2 (1.7)	8.8 (3.1)	5.8 (3.1)	5.2 (1.0)	5.6 (2.3)	4.4 (1.3)	5.8 (1.8)
95% CI of mean difference	(-2.5, 2.3)	(-4.3, 3.4)	(-11.3, 13.8)	(-3.5, 2.5)	(-2.8, 0.1)	(-3.7, 3.0)	(-3.2, 0.8)	(-5.5, 0.5)
p-value	0.9269	0.7966	0.7721	0.6884	0.0603	0.8115	0.2183	0.0925

of chemotherapy with several studies reporting the negative impact of hair loss on quality of life and psycho-social well-being [5,15,16]. It is of interest that 34% of women who were eligible for recruitment into our trial declined the use of SC suggesting that in some women, preventing hair loss is not a priority.

Scalp cooling has been used since the 1970s and in one of the largest published studies from the Dutch Scalp Cooling Registry, success was measured by the use of hair covering. The authors reported the highest rates of no hair covering worn in patients receiving monotherapy with taxanes (81%–94%) and the lowest with those receiving TAC chemotherapy (8%, as compared to 0% in the current study) [6]. A meta-analysis of various interventions used to prevent CIA demonstrated that scalp cooling was the most successful method, with a relative risk reduction of 0.38 (95% CI = 0.32–0.45), thus leading us to evaluate this intervention in the current study [3].

Our primary study endpoint was not reached for either the entire population or each subgroup according to chemotherapy regimen given. However, the success of SC was varied based on the type of chemotherapy given, with patients in the current study who received concurrent anthracycline and taxane having the lowest rate of minimal hair loss (20%). These results are similar to those of a recent study demonstrating a 22% rate of hair preservation with anthracycline-based regimen (doxorubicin, cyclophosphamide or doxorubicin, cyclophosphamide and fluorouracil) [17]. In contrast, higher rates of success were reported by two recent publications, where success with SC in patients receiving taxane-based regimens were in the order of 70% and 66% [17,18]. The lower rates of minimal hair loss in our study may be due to differences in the method used to report the degree of hair loss. Nangia et al. utilised blinded assessment of hair loss by the clinician, whilst in our study hair loss was reported by patients. Although the former study demonstrated a similar incidence of hair preservation as perceived by the patient (51%) as compared to that assessed by the physician (56%), these were not observations made in the same patient. Others have shown that clinician-rating of moderate to severe hair loss is usually lower when compared to self-reporting by patients (35% vs. 80%, respectively). [19] We found only a fair rate of agreement between the clinician and the patient, again with the clinician tending to report a lesser degree of hair loss than the patient. In the study by Rugo et al., patients were asked to rate the degree of hair loss by reviewing photos of their hair at each cycle compared to the baseline image, with the worse Dean score being used to assess success of SC. This latter method may have ensured a more

consistent objective assessment by patients, as compared to our study where patients were reporting subjective changes over time. As such, we suggest that future research into CIA should measure efficacy as perceived by the patient and adopt an objective assessment method.

Although others have demonstrated younger age and thinner hair as factors associated with greater success in minimising hair loss, we did not observe this in our study. In vitro data has demonstrated greater cytoprotection with scalp temperatures of 18 °C and 14 °C, but we could not demonstrate any difference in degree of hair loss based on randomisation to the two temperature settings within each cohort in our study.^{9,10} We recognize that we were unable to formally measure the scalp temperature to ascertain whether the lower cap temperature setting indeed achieved a lower scalp temperature. Further, the effect of lowering the SC temperature may not replicate the temperatures which were needed to demonstrate an effect on cultured keratinocytes in the laboratory.⁹

We failed to detect an independent impact of minimal hair loss on mood (anxiety or depression) or body image, although there was a trend for worsening body image in patients with severe hair loss. However, we noted that the baseline levels of moderate to severe anxiety (25%) and depression (14%) respectively, were reduced by the end of treatment. This was irrespective of the degree of hair loss, indicating that there are many other factors influencing a woman's mood following a diagnosis of breast cancer and receipt of chemotherapy, which was beyond the scope of this study to assess.

It is of interest that the majority of patients were satisfied with use of SC and would elect to use it again, irrespective of how effective the device had been. Anecdotally, many patients expressed their satisfaction with being offered an intervention to minimise hair loss. We suggest that the recognition of the impact of hair loss from chemotherapy by the treating clinician and being pro-active in offering a possible solution, is in itself a worthwhile management approach.

Overall, SC was tolerable with short-lived grade 1 adverse events which resolved in all cases. At a median follow-up of 22 months, no patients have developed scalp metastases. One patient in cohort one developed lung metastases at 12 months from diagnosis and to date has not developed scalp metastases.

In conclusion, our study provides the confirmatory evidence that women recommended for combination anthracycline and taxane chemotherapy, whether given concurrently or sequentially, have low rates of minimal hair loss and many patients in these two

cohorts did not persevere with using SC. Patients who receive a taxane-based regimen with or without carboplatin and trastuzumab, experienced the highest rates of minimal hair loss and the excellent compliance with SC for four or six cycles of chemotherapy reflect the tolerability of the device. Although our study could not demonstrate an independent benefit of minimal hair loss on mood and body image, we would routinely recommend the use of SC to women being recommended for taxane-based chemotherapy. For patients who are to receive anthracycline-taxane chemotherapy, an individualised approach should be taken, balancing the low rates of efficacy and longer treatment times against the importance of hair loss perceived by the patient.

Conflicts of interest

None to declare.

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