JAMA | Original Investigation

Effect of a Scalp Cooling Device on Alopecia in Women Undergoing Chemotherapy for Breast Cancer
The SCALP Randomized Clinical Trial

Julie Nangia, MD; Tao Wang, PhD; Cynthia Osborne, MD; Polly Niravath, MD; Kristen Otte, BA; Steven Papish, MD; Frankie Holmes, MD; Jame Abraham, MD; Mario Lacouture, MD; Jay Courtright, MD; Richard Paxman, BSc; Mari Rude, ANP; Susan Hilsenbeck, PhD; C. Kent Osborne, MD; Mothaffar Rimawi, MD

IMPORTANCE Chemotherapy may induce alopecia. Although scalp cooling devices have been used to prevent this alopecia, efficacy has not been assessed in a randomized clinical trial.

OBJECTIVES To assess whether a scalp cooling device is effective at reducing chemotherapy-induced alopecia and to assess adverse treatment effects.

DESIGN, SETTING, AND PARTICIPANTS Multicenter randomized clinical trial of women with breast cancer undergoing chemotherapy. Patients were enrolled from December 9, 2013, to September 30, 2016. One interim analysis was planned to allow the study to stop early for efficacy. Data reported are from the interim analysis. This study was conducted at 7 sites in the United States, and 182 women with breast cancer requiring chemotherapy were enrolled and randomized.

INTERVENTIONS Participants were randomized to scalp cooling (n = 119) or control (n = 63). Scalp cooling was done using a scalp cooling device.

MAIN OUTCOMES AND MEASURES The primary efficacy end points were successful hair preservation assessed using the Common Terminology Criteria for Adverse Events version 4.0 scale (grade 0 [no hair loss] or grade 1 [<50% hair loss not requiring a wig] were considered to have hair preservation) at the end of 4 cycles of chemotherapy by a clinician unaware of treatment assignment, and device safety. Secondary end points included wig use and scores on the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30, Hospital Anxiety and Depression Scale, and a summary scale of the Body Image Scale.

RESULTS At the time of the interim analysis, 142 participants were evaluable. The mean (SD) age of the patients was 52.6 (10.1) years; 36% (n = 51) received anthracycline-based chemotherapy and 64% (n = 91) received taxane-based chemotherapy. Successful hair preservation was found in 48 of 95 women with cooling (50.5%; 95% CI, 40.7%-60.4%) compared with 0 of 47 women in the control group (0%; 95% CI, 0%-7.6%) (success rate difference, 50.5%; 95% CI, 40.5%-60.6%). Because the 1-tailed *P* value from the Fisher exact test was <.001, which crossed the superiority boundary (*P* = .0061), the data and safety monitoring board recommended study termination on September 26, 2016. There were no statistically significant differences in changes in any of the scales of quality of life from baseline to chemotherapy cycle 4 among the scalp cooling and control groups. Only adverse events related to device use were collected; 54 adverse events were reported in the cooling group, all grades 1 and 2. There were no serious adverse device events.

CONCLUSIONS AND RELEVANCE Among women with stage I to II breast cancer receiving chemotherapy with a taxane, anthracycline, or both, those who underwent scalp cooling were significantly more likely to have less than 50% hair loss after the fourth chemotherapy cycle compared with those who received no scalp cooling. Further research is needed to assess longer-term efficacy and adverse effects.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01986140

JAMA. 2017;317(6):596-605. doi:10.1001/jama.2016.20939

Editorial page 587

Author Audio Interview

Related article page 606 and JAMA Patient Page page 656

Supplemental content

CME Quiz at jamanetworkcme.com and CME Questions oage 641

Related article at jamaoncology.com

Author Affiliations: Baylor College of Medicine, Houston, Texas (Nangia, Wang, Niravath, Otte, Rude, Hilsenbeck, C. K. Osborne, Rimawi); Texas Oncology, US Oncology, Dallas (C. Osborne, Holmes, Courtright); Now with The Methodist Hospital, Houston, Texas (Niravath); Summit Medical Group–MD Anderson Cancer Center, Morristown, New Jersey (Papish); Cleveland Clinic, Cleveland, Ohio (Abraham); Memorial Sloan Kettering Cancer Center, New York, New York (Lacouture); Paxman Coolers Ltd, Huddersfield, England (Paxman).

Corresponding Author: Julie Nangia, MD, Baylor College of Medicine, One Baylor Plaza, BCM 660, Houston, TX 77030 (nangia@bcm.edu).

Copyright 2017 American Medical Association. All rights reserved.

Downloaded From: on 01/18/2018

In breast cancer, chemotherapy treats micrometastatic disease and decreases the risk of recurrence. However, chemotherapy may be associated with adverse effects such as chemotherapy-induced alopecia, which women rate as one of the most distressing adverse effects of chemotherapy.[1,2] In many countries, scalp cooling is used to prevent alopecia. Rapidly growing cells such as cancer and hair follicles are more susceptible to chemotherapy.[3,4] Scalp cooling is hypothesized to cause cutaneous vasoconstriction in the scalp, which reduces blood flow to the hair follicles and therefore reduces uptake of chemotherapeutic agents. It also reduces biochemical activity, which may make hair follicles less susceptible to the damage of chemotherapy.[3,4] Modern methods to prevent hair loss use devices that circulate fluid in a cooling cap using refrigeration. A cap is placed on the patient prior to chemotherapy and does not have to be changed or removed until the treatment is completed. Historically, success rates with scalp cooling have been variable, but nonrandomized studies suggest scalp cooling devices may be associated with less chemotherapy-induced alopecia.[3,4]

As scalp cooling acts by reducing the effect of chemotherapy in the scalp, a theoretical increase in the risk of scalp metastases is often discussed.[5,6] Published data demonstrate that the incidence of scalp metastasis following chemotherapy in breast cancer is low, and it is exceedingly rare for the scalp to be the first site of metastases.[7,8] However, long-term safety data from other countries only recently became available,[3,5,9] and it was this concern that previously prevented the study and use of scalp cooling devices in the United States.

The purpose of this clinical trial was to assess whether use of the Orbis Paxman Hair Loss Prevention System, a scalp cooling device, is safe and effective in reducing chemotherapy-induced alopecia in woman with breast cancer undergoing neoadjuvant or adjuvant chemotherapy. As a secondary outcome, it was hypothesized based on data from several studies[4,10-14] that women who did not have clinically significant chemotherapy-induced alopecia would have better quality of life compared with women with chemotherapy-induced alopecia.

Key Points

Question What is the effectiveness of a scalp cooling device in preventing alopecia in women with breast cancer undergoing neoadjuvant or adjuvant chemotherapy?

Findings In a randomized clinical trial of 182 women with breast cancer receiving chemotherapy with a taxane, anthracycline, or both, those who underwent scalp cooling were significantly more likely to have less than 50% hair loss compared with no scalp cooling (50.5% vs 0%). The trial was stopped early for superiority, and there was no effect on measures of quality of life.

Meaning This scalp cooling system was more likely to prevent alopecia than no treatment, and further research is needed to assess longer-term efficacy and adverse effects.

Methods

Study Design and Patients

The Scalp Cooling Alopecia Prevention (SCALP) trial was a multicenter, randomized, nonblinded study conducted from December 9, 2013, to September 30, 2016, for women planning to undergo neoadjuvant or adjuvant chemotherapy. This trial was open at 7 sites across the United States: Baylor College of Medicine, Cleveland Clinic, Memorial Sloan Kettering Cancer Center, and 4 US Oncology Network sites (Baylor Sammons Cancer Center, Texas Oncology-Medical City Dallas, Texas Oncology-Houston Memorial City, and Hematology & Oncology Associates of Northern New Jersey [which is now Summit Medical Group-MD Anderson Cancer Center]). The protocol was approved by the institutional review board at each site, and all patients provided written informed consent to participate in this clinical trial. The full trial protocol is available in Supplement 1. Baylor College of Medicine was the lead site and performed all the data management, monitoring, and data analysis for this clinical trial.

Key eligibility criteria were having stage I or II breast cancer and planning to receive at least 4 cycles of taxane- and/or anthracycline-based chemotherapy for curative intent. Key exclusion criteria were Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0) alopecia grade higher than 0, prior chemotherapy, history of migraine headaches, hypothyroidism, hepatitis, uncontrolled diabetes, severe anemia, and anorexia.

Changes to the clinical trial after commencement included allowing more chemotherapy regimens that are commonly used to treat breast cancer (still taxane- or anthracycline-based); allowing pertuzumab, which is a non-chemotherapy agent not associated with hair loss; adding an interim analysis (memorandum with complete analysis plan issued on July 8, 2015); allowing a lower hemoglobin level to account for blood loss during surgery; increasing the allowed number of clinical sites from 5 to up to 10; and clarifications to the protocol. Race and ethnicity data were collected by self-report.

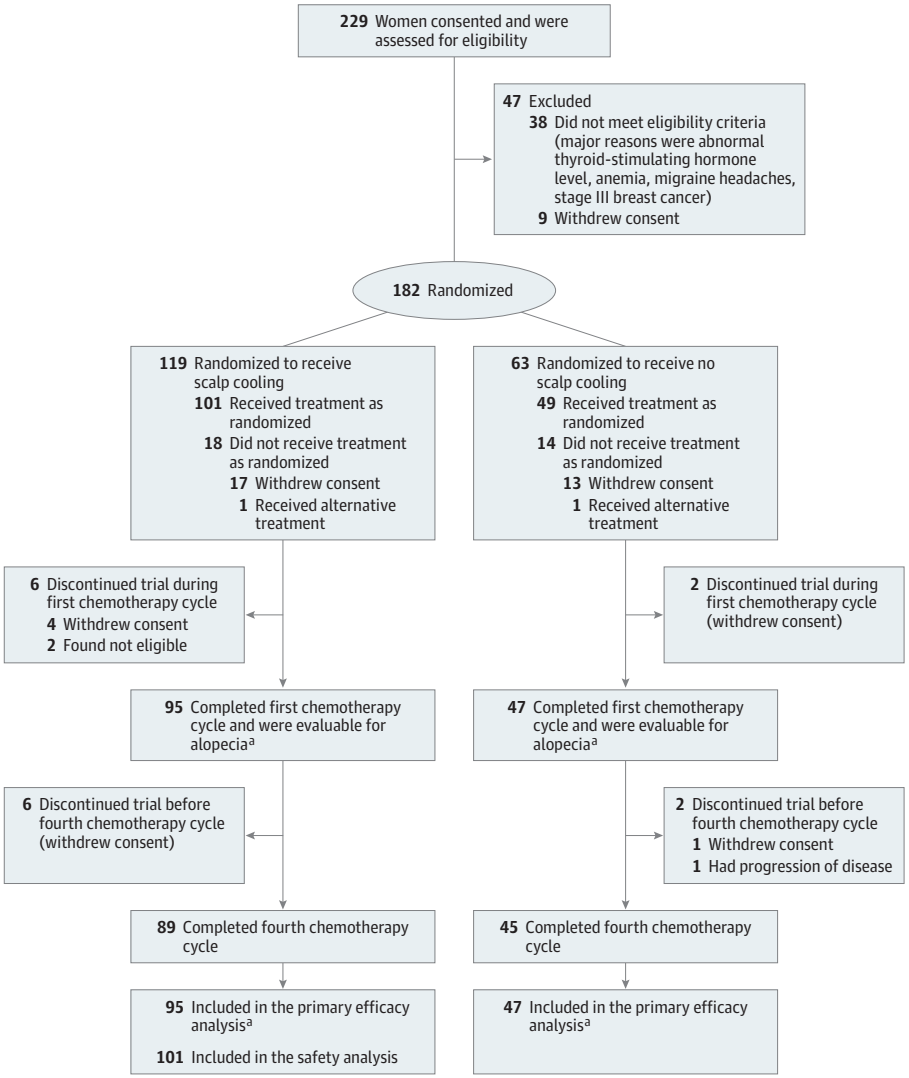
Randomization and Intervention

Randomization was performed centrally at the lead site using the Oracle database-backed web application that made assignments based on a computer-generated random number. Participants were stratified by clinical site (6 of the 7 active sites had accrued patients who were part of this interim analysis) and major type of chemotherapy (anthracycline or taxane), then randomized in a 2:1 ratio to the scalp cooling device or to no scalp cooling (control) (**Figure**). Permuted blocks were used with a block size of 6: 4 in the experimental group and 2 in the control group. The lead site randomized and entered all patients in the study in real time after determining eligibility and communicated assignments back to the sites. At the time of the interim analysis, 182 participants were randomized; of them, 30 withdrew after being randomized but before starting chemotherapy, 6 withdrew before completing 1 cycle of chemotherapy, and 7 withdrew after completing the first cycle.

Copyright 2017 American Medical Association. All rights reserved.

Downloaded From: on 01/18/2018

Figure. Participant Flow Diagram of the SCALP Trial, December 9, 2013, Through September 30, 2016, at the Interim Analysis



A cycle of chemotherapy is 2 to 3 weeks long depending on the chemotherapy regimen used (defined by regimen in the protocol).

[a] The population included in the primary efficacy analysis is composed of participants who were randomized and completed at least 1 cycle of chemotherapy.

Scalp cooling using a scalp cooling device was done 30 minutes prior to and during and 90 minutes after each chemotherapy infusion. For participants receiving scalp cooling, a comfort scale[4] was administered after each treatment. Alopecia assessments using the CTCAE v4.0 were completed at baseline and after each cycle of chemotherapy by a clinician blinded to treatment assignment, by the participant's clinician, and by the participant. Participants were also asked if they needed to use a wig and/or a head wrap with each alopecia assessment. The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30), Hospital Anxiety and Depression Scale (HADS), and Body Image Scale (BIS) questionnaires were completed by participants at baseline, after 4 cycles of chemotherapy, and at completion of chemotherapy if the participant received more than 4 cycles of chemotherapy. Study participants will be followed up at routine follow-up visits for 5 years after the study for safety (time and site of first recurrence) and overall survival.

Outcomes

The primary efficacy end point was success in hair preservation after the fourth cycle of chemotherapy. Success was defined as CTCAE v4.0 alopecia grade 0 (no hair loss) or grade 1 (<50% hair loss not requiring a wig). Failure was defined as CTCAE v4.0 grade 2 (>50% hair loss, requiring use of a wig) (eFigure 1 in Supplement 2). The primary efficacy end point was assessed by clinicians who were independent and unaware of study treatment. Participant withdrawals from the study were deemed treatment failures. The exploratory secondary efficacy end points were success in hair preservation assessed by the participant's clinician and by the participant; use of wigs and/or head wraps; participant-reported comfort; and quality of life.

Copyright 2017 American Medical Association. All rights reserved.

Downloaded From: on 01/18/2018

Quality of life was assessed by the EORTC QLQ-C30 (emotional functioning scale and social functioning scale), HADS (anxiety summary and depression summary), and BIS (body image scale). The emotional functioning scale score was calculated from EORTC QLQ-C30 items 21 through 24 and the social functioning scale score was calculated from EORTC QLQ-C30 items 26 and 27 using the EORTC QLQ-C30 scoring formula, which linearly transformed the average of raw scores to a range from 0 to 100 (a higher score represented a higher or better level of functioning). Any missing questionnaire items in the functioning scale calculation were replaced by the average of nonmissing items if less than half of the items from the functioning scale were missing. A change in the functioning scale score of 5 to 10 is considered "a little" change for better or worse; a change of greater than 10 to 20 is considered a "moderate" change; and a change greater than 20 is considered a "very much" change.[15] The HADS was used to assess anxiety and depression. It includes 7 questions to assess anxiety and 7 to assess depression. The summary scores (sum of the 7 question items) for anxiety and depression each ranged from 0 to 21: scores of 0 to 7 were considered normal, 8 to 10 were considered borderline abnormal (borderline case), and 11 to 21 were considered abnormal (case). Missing items were replaced by the average of nonmissing items if only 1 item from the anxiety or depression scale was missing.[16] The BIS summary score was the sum of the first 9 (of 10) items in the BIS. The last item in the BIS for scar was not applicable to the study participants, so it was not included. The summary score ranged from 0 to 27; a score of 0 indicated no symptoms or distress, and a higher score indicated increasing symptoms or distress. Missing items were replaced by the average of nonmissing items if only 1 or 2 items from the 9 items in the BIS were missing.[17]

The primary safety end point was anticipated adverse device effects, as the complications were known to be associated with use of scalp cooling devices. Anticipated adverse device effects included cold discomfort, headache, forehead pain, dizziness, and nausea described in CTCAE v4.0. The secondary safety end points were participant-reported comfort scale score and early scalp metastases and survival. Participant-reported comfort was categorized into 5 levels: very comfortable, reasonably comfortable, comfortable, uncomfortable, and very uncomfortable.[4] Participants will be followed up for 5 years for overall survival and first recurrence, including isolated scalp metastases. Time to recurrence or overall survival will be measured from the date of randomization to the date of first recurrence or the date of death. Participants without recurrence or death were considered as censored at the last contact date.

Statistical Analysis

We planned to enroll 235 participants to provide 85% power to detect, using Fisher exact test, a 20% absolute difference in hair preservation (ie, 15% with no cooling vs 35% with scalp cooling). There have been no randomized studies to date; in observational studies the rate of hair retention has been variable, with rates from 0% to 90%.[18] This trial was designed to detect a 20% absolute difference in hair preservation (1 in 5 participants), which would also be a clinically meaningful outcome. One interim analysis was planned to allow the study to stop early for efficacy (superiority) after 95 and 47 patients had been enrolled to cooling or no cooling, respectively, and had been evaluated for the primary end point. To maintain the overall type I error rate, an O'Brien-Fleming spending function was used to set the superiority boundaries (interim boundary was calculated as $P = .0061$, or $Z = 2.509$).

All analyses for efficacy were based on the modified intent-to-treat population, defined as eligible and randomized participants who underwent at least 1 cycle of chemotherapy. The primary efficacy analysis compared the success of hair preservation between scalp cooling with the device and control (no scalp cooling) after 4 cycles of chemotherapy using Fisher exact test. Cochran-Mantel-Haenszel test and a multivariable logistic regression model were used to explore the treatment effect after adjusting for clinical site and chemotherapy. The success rates varied across the sites and by major chemotherapy type, so site and chemotherapy were added to the statistical models. Because the control group had no success in hair preservation, the maximum likelihood estimates did not exist. Data were analyzed using a logistic regression model with penalized maximum likelihood estimation. Independent variables included treatment group, sites, and major chemotherapy type. The results showed that these were all significant variables associated with the outcome of hair loss. Planned exploratory secondary analyses summarized perceived hair preservation on the basis of participant (assessed by the CTCAE v4.0 and an alopecia pictorial tool) and use of wigs and/or head wraps by descriptive statistics with rates and their 95% confidence intervals, and changes from baseline to the fourth cycle of chemotherapy in quality of life assessed by the EORTC QLQ-C30, HADS, and BIS questionnaires were compared using Wilcoxon rank sum tests or Kruskal-Wallis tests. Safety analyses were planned to report frequencies of device-associated adverse events, including serious adverse device effects and unanticipated adverse device effects. Unless otherwise specified, 2-sided statistical tests were used and $P \leq .05$ was considered statistically significant. All analyses were performed in SAS version 9.4 statistical software (SAS Institute Inc).

Results

Between December 9, 2013, and September 30, 2016, 229 participants were enrolled and provided written informed consent for the SCALP clinical trial at 7 sites across the United States. Of these 229 participants, 182 were randomized to scalp cooling or control. Of the 182 randomized participants, 142 participants who completed at least 1 cycle of chemotherapy were evaluable for the primary end point and composed the modified intent-to-treat population (Figure). A preplanned interim analysis was performed, and the data from the participants in this interim analysis are reported herein.

Baseline demographic data and clinical characteristics in each group are summarized in **Table 1**. The treatment and

Copyright 2017 American Medical Association. All rights reserved.

Downloaded From: on 01/18/2018

Table 1. Demographic Information and Baseline Characteristics

Parameter	Randomized Population			Modified ITT Population[a]		
	Cooling (n = 119)	Noncooling (n = 63)	All (n = 182)	Cooling (n = 95)	Noncooling (n = 47)	All (n = 142)
Age, y						
Mean (SD)	52.1 (9.8)	52.2 (10.1)	52.1 (9.9)	52.4 (10.2)	52.9 (10.0)	52.6 (10.1)
Median (range)	53 (27-69)	51 (33-70)	52.5 (27-70)	53 (27-69)	55 (33-70)	54 (27-70)
Race, No. (%)						
White	102 (85.7)	49 (77.8)	151 (83)	81 (85.3)	35 (74.5)	116 (81.7)
Black or African American	13 (10.9)	9 (14.3)	22 (12.1)	10 (10.5)	7 (14.9)	17 (12.0)
Asian	4 (3.4)	5 (7.9)	9 (4.9)	4 (4.2)	5 (10.6)	9 (6.3)
Ethnicity, No. (%)						
Hispanic or Latina	21 (17.6)	9 (14.3)	30 (16.5)	16 (16.8)	8 (17.0)	24 (16.9)
Non-Hispanic	98 (82.4)	54 (85.7)	152 (83.5)	79 (83.2)	39 (83.0)	118 (83.1)
CTCAE v4.0 alopecia grade 0 at baseline, No. (%)	119 (100)	63 (100)	182 (100)	95 (100)	47 (100)	142 (100)
Major chemotherapy type, No. (%)						
Anthracycline	41 (34.5)	22 (34.9)	63 (34.6)	32 (33.7)	19 (40.4)	51 (35.9)
Taxane	78 (65.5)	41 (65.1)	119 (65.4)	63 (66.3)	28 (59.6)	91 (64.1)
Study site, No. (%)[b]						
1	27 (22.7)	13 (20.6)	40 (22.0)	19 (20.0)	11 (23.4)	30 (21.1)
2	63 (52.9)	34 (54.0)	97 (53.3)	51 (53.7)	25 (53.2)	76 (53.5)
3	8 (6.7)	4 (6.3)	12 (6.6)	8 (8.4)	3 (6.4)	11 (7.7)
4	13 (10.9)	6 (9.5)	19 (10.4)	11 (11.6)	5 (10.6)	16 (11.3)
5	7 (5.9)	5 (7.9)	12 (6.6)	5 (5.3)	2 (4.3)	7 (4.9)
6	1 (0.8)	1 (1.6)	2 (1.1)	1 (1.1)	1 (2.1)	2 (1.4)
Breast cancer stage, No. (%)						
I	46 (38.7)	25 (39.7)	71 (39.0)	38 (40.0)	19 (40.4)	57 (40.1)
II	73 (61.3)	38 (60.3)	111 (61.0)	57 (60.0)	28 (59.6)	85 (59.9)
Scheduled chemotherapy regimen, No. (%)						
Doxorubicin, 60 mg/m^2, with cyclophosphamide, 600 mg/m^2	39 (32.8)	20 (31.7)	59 (32.4)	30 (31.6)	17 (36.2)	47 (33.1)
Doxorubicin, 50 mg/m^2, with fluorouracil, 500 mg/m^2, and cyclophosphamide, 500 mg/m^2	2 (1.7)	2 (3.2)	4 (2.2)	2 (2.1)	2 (4.3)	4 (2.8)
Paclitaxel, 80-90 mg/m^2 weekly (every 3 wk constitutes a cycle), or 175 mg/m^2 every 2-3 wk as a single agent	6 (5.0)	6 (9.5)	12 (6.6)	5 (5.3)	5 (10.6)	10 (7.0)
Paclitaxel, 80-90 mg/m^2 weekly, with carboplatin target AUC of 6 mg · min/mL every 3 wk	1 (0.8)	0	1 (0.5)	1 (1.1)	0	1 (0.7)
Docetaxel, 100 mg/m^2, as a single agent	2 (1.7)	3 (4.8)	5 (2.7)	1 (1.1)	2 (4.3)	3 (2.1)
Docetaxel, 75-100 mg/m^2, with pertuzumab and trastuzumab at standard doses	3 (2.5)	1 (1.6)	4 (2.2)	1 (1.1)	1 (2.1)	2 (1.4)
Docetaxel, 75 mg/m^2, with cyclophosphamide, 600 mg/m^2	40 (33.6)	18 (28.6)	58 (31.9)	34 (35.8)	9 (19.1)	43 (30.3)
Docetaxel, 75 mg/m^2, with carboplatin target AUC of 6 mg · min/mL, and trastuzumab at standard doses	26 (21.8)	13 (20.6)	39 (21.4)	21 (22.1)	11 (23.4)	32 (22.5)

(continued)

Copyright 2017 American Medical Association. All rights reserved.

Downloaded From: on 01/18/2018

Table 1. Demographic Information and Baseline Characteristics (continued)

Parameter	Randomized Population			Modified ITT Population[a]		
	Cooling (n = 119)	Noncooling (n = 63)	All (n = 182)	Cooling (n = 95)	Noncooling (n = 47)	All (n = 142)
ECOG performance status, No. (%)						
Fully active	112 (94.1)	53 (84.1)	165 (90.7)	91 (95.8)	39 (83.0)	130 (91.5)
Restricted	4 (3.4)	6 (9.5)	10 (5.5)	3 (3.2)	4 (8.5)	7 (4.9)
Ambulatory	0	2 (3.2)	2 (1.1)	0	2 (4.3)	2 (1.4)
Not reported	3 (2.5)	2 (3.2)	5 (2.7)	1 (1.1)	2 (4.3)	3 (2.1)

Abbreviations: AUC, area under the curve; CTCAE v4.0, Common Terminology Criteria for Adverse Events version 4.0; ECOG, Eastern Cooperative Oncology Group; ITT, intent-to-treat.

[a] Defined as eligible and randomized participants in the interim analysis who underwent at least 1 cycle of chemotherapy.

[b] The seventh study site recently opened and had no patients included in the interim analysis.

Table 2. Summary of Success in Hair Preservation Assessed by Clinician in Modified Intent-to-Treat Population[a]

Parameter	Cooling (n = 95)		Noncooling (n = 47)	
	No.	% (95% CI)	No.	% (95% CI)
Hair preservation[b]				
Success[c]	48	50.5 (40.7-60.4)	0	0 (0-7.6)
Alopecia grade 0	5	5.3		
Alopecia grade 1	43	45.3		
Failure	47	49.5 (39.6-59.4)	47	100 (92.4-100)
Hair preservation at study site[d,e]				
Site 1				
Success	2	10.5 (2.9-31.4)	0	0 (0-25.9)
Failure	17	89.5 (68.6-97.1)	11	100 (74.1-100)
Site 2				
Success	35	68.6 (55.0-79.7)	0	0 (0-13.3)
Failure	16	31.4 (20.3-45.0)	25	100 (86.7-100)
Site 3				
Success	1	12.5 (2.2-47.1)	0	0 (0-56.1)
Failure	7	87.5 (52.9-97.8)	3	100 (43.9-100)
Site 4				
Success	7	63.6 (35.4-84.8)	0	0 (0-43.4)
Failure	4	36.4 (15.2-64.6)	5	100 (56.6-100)
Site 5				
Success	3	60.0 (23.1-88.2)	0	0 (0-65.8)
Failure	2	40.0 (11.8-76.9)	2	100 (34.2-100)
Site 6				
Success	0	0 (0-79.3)	0	0 (0-79.3)
Failure	1	100 (20.7-100)	1	100 (20.7-100)

[a] The modified intent-to-treat population was defined as eligible and randomized participants in the interim analysis who underwent at least 1 cycle of chemotherapy.

[b] Hair preservation was graded according to Common Terminology Criteria for Adverse Events version 4.0. Grade 0 or 1 alopecia was considered success; grade 2 alopecia was considered failure.

[c] Success rate difference was 50.5% (95% CI, 40.5%-60.6%; Fisher exact test, 1-tailed $P < .001$).

[d] The seventh study site recently opened and had no patients included in the interim analysis.

[e] Cochran-Mantel-Haenszel test, $P < .001$.

control groups were generally comparable. In the modified intent-to-treat population, the mean (SD) age was 52.6 (10.1) years; 64% of participants (n = 91) received taxane-based chemotherapy and 36% (n = 51) received anthracycline-based chemotherapy. At the time of the interim analysis, 95 patients in the cooling group and 47 patients in the no cooling group were evaluable and had completed 4 cycles of chemotherapy. The mean age and other demographic variables of the patients included in the interim analysis and of the participants who received taxane-based or anthracycline-based chemotherapy were similar to those of the entire group enrolled (Table 1).

Among the patients in the interim analysis, 48 of 95 women in the cooling group (50.5%; 95% CI, 40.7%-60.4%) and 0 of 47 women in the control group (0%; 95% CI, 0%-7.6%) had hair preservation (**Table 2**). The success rate difference between the 2 groups was 50.5% (95% CI, 40.5%-60.6%). The 1-tailed *P* value from the Fisher exact test was <.001, which crossed the superiority boundary ($P = .0061$). Thus, on September 26, 2016, the data and safety monitoring board agreed with the recommendations from the statistician to stop accrual to the study early and release the results to the principal investigator owing to superiority of hair retention in the participants who received scalp cooling vs the

Copyright 2017 American Medical Association. All rights reserved.

Downloaded From: on 01/18/2018

Table 3. Summary of Quality-of-Life Data in the Modified Intent-to-Treat Population[a]

	Cooling (n = 94)						Noncooling (n = 47)			
	Hair Preservation, Median (IQR) (n = 48)			No Hair Preservation, Median (IQR) (n = 46)			No Hair Preservation, Median (IQR) (n = 47)			
Parameter	Baseline (n = 48)	After Cycle 4 (n = 48)	Change From Baseline[b]	Baseline (n = 46)	After Cycle 4 (n = 32)	Changes From Baseline[b]	Baseline (n = 47)	After Cycle 4 (n = 38)	Change From Baseline[b]	*P* Value[c]
EORTC QLQ-C30 score[d]										
Emotional functioning	83.3 (66.7 to 91.7)	83.3 (66.7 to 91.7)	0 (−12.5 to 16.7)	75.0 (58.3 to 91.7)	75 (66.7 to 91.7)	0 (−8.3 to 25.0)	83.3 (66.7 to 100)	83.3 (75.0 to 100)	0 (−8.3 to 8.3)	.54
Social functioning	83.3 (66.7 to 100)	83.3 (66.7 to 100)	0 (−16.7 to 0)	83.3 (66.7 to 100)	83.3 (66.7 to 100)	0 (−16.7 to 0)	100 (83.3 to 100)	100 (66.7 to 100)	0 (−33.3 to 0)	.56
HADS score[e]										
Anxiety summary	5 (3 to 8)	4 (2 to 7)	0 (−3 to 2)	5 (3 to 11)	4 (3 to 7)	−0.3 (−4 to 1)	5 (3 to 8)	3 (1 to 7)	−1.5 (−3 to 0)	.58
Depression summary	1 (0 to 3)	3 (2 to 5.5)	2 (0 to 4)	2 (0 to 4)	3 (1 to 6)	1 (0 to 2.5)	1 (1 to 5)	2 (1 to 5)	0 (0 to 2)	.15
BIS items 1-9 summary score[f]	3.5 (1 to 7)	5 (2.5 to 10.5)	2 (0 to 5)	2.5 (0 to 8)	7 (4 to 11.3)	1 (0 to 4)	2 (0 to 4)	5 (2 to 9)	2 (0 to 4)	.71

Abbreviations: BIS, Body Image Scale; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30; HADS, Hospital Anxiety and Depression scale; IQR, interquartile range.

[a] The modified intent-to-treat population was defined as eligible and randomized participants in the interim analysis who underwent at least 1 cycle of chemotherapy.

[b] Changes were calculated by the scores at chemotherapy cycle 4 minus the scores at baseline.

[c] Kruskal-Wallis test was used to compare the changes among the 3 groups.

[d] Scores range from 0 to 100 (a higher score represents a higher or better level of functioning).

[e] Scores range from 0 to 21. Scores of 0 to 7 were considered normal; 8 to 10, borderline abnormal (borderline case); and 11 to 21, abnormal (case).

[f] Scores range from 0 to 27. A score of 0 indicates no symptoms or distress; a higher score, increasing symptoms or distress.

group not receiving scalp cooling. Preservation in the cooling group was statistically higher than that in the control group ($P < .001$ by Cochran-Mantel-Haenszel test).

There were substantial differences in success of hair preservation by site (Table 2) and by drug group (taxane vs anthracycline; eTable 1 in Supplement 2). Success ranged from 0% (n = 1 in the cooling group) to 68.6% (n = 51 in the cooling group). In an exploratory post hoc analysis (eTable 2 in Supplement 2) that accounted for site effects, the estimated rate of hair preservation with anthracycline-based chemotherapy was 16% (95% CI, 4%-46%), and with taxanes was 59% (95% CI, 27%-84%) (eFigure 2 in Supplement 2).

Rates of participant-perceived hair retention were 48 of 95 women in the cooling group (50.5%; 95% CI, 40.7%-60.4%) and 0 of 47 women in the control group (0%; 95% CI, 0%-7.6%). Rates of oncologist-graded hair preservation were 53 of 95 women in the cooling group (55.8%; 95% CI, 45.8%-65.4%) and 0 of 47 women in the control group (0%; 95% CI, 0%-7.6%). Wigs or head wraps were used by 63% (95% CI, 53%-72%) of the patients who received scalp cooling and 100% (95% CI, 92.4%-100%) of those who were in the control group.

Quality of Life

The change in emotional functioning and social functioning after 4 cycles of chemotherapy was not significantly different for the patients in the cooling group with hair preservation (n = 48), patients in the cooling group without hair preservation (n = 46), and patients in the noncooling group (n = 47) (**Table 3**). The HADS anxiety and depression summary scores were normal (<7) at baseline and after 4 cycles in both the cooling group (with and without hair preservation) and the noncooling group. The median BIS summary scores ranged from 2 to 3.5 at baseline and from 5 to 7 after 4 cycles of chemotherapy among the participants, with no significant difference between the 3 groups.

Adverse Events

Only adverse events related to device use were collected, and no adverse events known to be associated with chemotherapy were collected. There were 54 adverse events reported in the cooling group: 46 anticipated adverse device effects and 8 unanticipated adverse device effects. There were no serious adverse device events. All adverse events were grade 1 (n = 46) or grade 2 (n = 8), and these included chills, dizziness, headache, nausea, paresthesia, pruritus, sinus pain, skin and subcutaneous tissue disorders, and skin ulceration (**Table 4**). Of the grade 2 adverse device events, 7 were headache and 1 was scalp pain. The only unanticipated adverse events were dry skin and scalp pain. Based on the comfort scale, most patients were comfortable, reasonably comfortable, or very comfortable while wearing the device, with a median rating of reasonably comfortable. Of note, there were 6 participants not included in this safety analysis who withdrew consent during the precooling process: 4 because the device was too cold or uncomfortable, 1 due to anxiety, and 1 due to claustrophobia from the device. There was also 1 participant who withdrew during the chemotherapy prior to completing 1 cycle of chemotherapy because the device was too cold. These participants are not part of the modified intent-to-treat population as they did not complete

Copyright 2017 American Medical Association. All rights reserved.

Downloaded From: on 01/18/2018

Table 4. Summary of Adverse Device Effects in the Safety Analysis[a]

Adverse Device Event	Participants by Chemotherapy Cycle, No. (%)			
	1 (n = 101)	2 (n = 84)	3 (n = 66)	4 (n = 62)
Headache	12 (11.9)	9 (10.7)	1 (1.5)	4 (6.5)
Nausea	4 (4.0)	2 (2.4)	1 (1.5)	1 (1.6)
Dizziness	3 (3.0)	1 (1.2)	0	0
Chills	1 (1.0)	0	0	0
Paresthesia	1 (1.0)	0	0	0
Pruritus	1 (1.0)	0	0	0
Sinus pain	0	0	1 (1.5)	0
Skin and subcutaneous tissue disorders	1 (1.0)	0	0	0
Skin ulceration	1 (1.0)	0	0	0
Dry skin	1 (1.0)	1 (1.2)	1 (1.5)	0
Scalp pain	1 (1.0)	2 (2.4)	1 (1.5)	1 (1.6)

[a] All adverse device events were graded using the Common Terminology Criteria for Adverse Events version 4.0. A total of 54 adverse events were reported: 44 patient-cycles had 46 anticipated adverse device effects and 8 patient-cycles had 8 unanticipated adverse device effects. There were no serious adverse events or serious adverse device events. All adverse events were grade 1 (n = 46) or grade 2 (n = 8). For analysis purposes, within each adverse device event and cycle, each patient was counted once, and patients with the same adverse event within a chemotherapy cycle were counted at the highest reported grade. Of 101 participants in the cooling group, 28 (27.7%) had at least 1 adverse event.

1 cycle of chemotherapy. Sixty additional participants were enrolled in this clinical trial, and the last participant is expected to complete chemotherapy in February 2017. A final analysis is planned at that time.

Discussion

In this study of women with breast cancer undergoing chemotherapy with a taxane, with an anthracycline, or with both agents, patients who received scalp cooling were significantly more likely than patients who did not receive scalp cooling to have less than 50% hair loss (with 50% of those in the scalp cooling group retaining their hair, compared with 0% of those in the control group). This is consistent with results from observational studies.[4,19-31] It is unclear why no differences emerged in various measures of quality of life between women who retained their hair and those who did not.

There was variability in the rate of hair preservation by site. This may be due to several factors, including the proper fitting of the cap, type of chemotherapy, and intrinsic patient characteristics. The fit of the cap is key to successful hair retention with the scalp cooling device, and there is a learning curve with use of the device; with repeated use, clinicians become more skilled at ensuring a tight fit and there is a higher likelihood of hair retention. After this clinical trial started, with more experience it was easier to train others on cap fitting. Thus, sites that opened later had better advice on ensuring a tight cap fit, which may have led to higher rates of hair retention. There was also a research coordinator's meeting in May 2015 at which retraining of cap fitting was performed, including techniques on how to better apply external pressure to improve cap fit. Another factor accounting for variable results may be different patient characteristics such as biochemical characteristics of hair from people of different ethnicities and hair thickness.[21] Studies in other countries have shown that different chemotherapy regimens have different rates of hair preservation success. For example, there were higher rates of hair preservation with taxane- vs anthracycline-based chemotherapy, and certain taxane-based chemotherapy regimens such as weekly paclitaxel have higher rates of hair preservations vs every-3-week docetaxel.[21,32] In this study, sites that had higher rates of taxane use also had higher rates of hair retention (59% vs 16%; eTable 2 in Supplement 2). The other US trial that is nonrandomized and used only taxane-based chemotherapy showed a similar hair retention rate of 66.3%.[31] If scalp cooling becomes widely used in the United States, decisions about type of chemotherapy may be informed by rates of hair retention with use of scalp cooling devices: for example, with ERBB2-positive breast cancer, a patient and physician weighing options for chemotherapy (docetaxel, carboplatin, and trastuzumab [TCH] for 6 cycles vs doxorubicin and cyclophosphamide for 4 cycles followed by docetaxel and trastuzumab for 4 cycles [AC→TH]) may consider the fact that TCH chemotherapy has higher rates of hair preservation. Cost may also be used in decision making about use of scalp cooling devices. Currently, scalp cooling devices in the United States cost about $1500 to $3000 total per patient and are not reimbursed by health insurance.

Statistical analysis of the questionnaires assessing quality of life did not show any differences in the group that received scalp cooling vs the control group or in the hair retention group vs alopecia group. This may be due to many reasons, including the distressing nature of a breast cancer diagnosis and treatment, changes in body image due to surgery and toxic effects from chemotherapy, and the lack of validated quality-of-life tools that are specifically designed to evaluate the quality-of-life effects of alopecia. Review of the literature shows that chemotherapy-induced alopecia is an important problem to patients with cancer, ranking among the most distressing adverse effects. Women have reported

Copyright 2017 American Medical Association. All rights reserved.

Downloaded From: on 01/18/2018

decreases in self-esteem, sexuality, and body image related to chemotherapy-induced alopecia; some women have even described having chemotherapy-induced alopecia as being more difficult than losing a breast. Better quality-of-life tools need to be developed to fully evaluate the effects of chemotherapy-induced alopecia on body image and psyche, but studies confirm that it is a concerning adverse effect.[33] The use of scalp cooling devices may help to alleviate some of this distress.

This study has several limitations, including variability of results at each site, assessing for successful hair retention after only 4 cycles of chemotherapy, and decreased power by stopping the trial early. Due to this heterogeneity in efficacy among treatment sites, the ultimate efficacy may be less than 50% at some sites where more anthracycline-based chemotherapy is administered or where there is less expertise in cap fitting. The primary efficacy end point was hair retention after 4 cycles of chemotherapy; therefore, participants who receive more than 4 cycles of chemotherapy, particularly with anthracyclines, may also have lower rates of hair retention. By stopping the trial early, the power to detect any difference in the end points, including adverse events, will be reduced with fewer patients and the 95% confidence interval will be larger. Substantial site differences and learning effects may influence how effective the intervention will be in clinical practice.

Overall, the scalp cooling device was well tolerated with no serious adverse device events, and most participants thought it was reasonably comfortable. Because of the concern of scalp metastases, study participants will continue to be followed up at routine follow-up visits for 5 years after the study for safety (time and site of first recurrence) and overall survival.

Conclusions

Among women with stage I to II breast cancer receiving chemotherapy with a taxane, anthracycline, or both, those who underwent scalp cooling were significantly more likely to have less than 50% hair loss after the fourth chemotherapy cycle compared with those who received no scalp cooling. Further research is needed to assess longer-term efficacy and adverse effects.

ARTICLE INFORMATION

Author Contributions: Drs Nangia and Hilsenbeck had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Nangia, Paxman, Rude, Hilsenbeck, C. K. Osborne, Rimawi.
Acquisition, analysis, or interpretation of data: Wang, C. Osborne, Niravath, Otte, Papish, Holmes, Abraham, Lacouture, Courtright, Rude, Hilsenbeck, C. K. Osborne, Rimawi.
Drafting of the manuscript: Nangia, Abraham, Lacouture, Hilsenbeck, C. K. Osborne, Rimawi.
Critical revision of the manuscript for important intellectual content: Nangia, Wang, C. Osborne, Niravath, Otte, Papish, Holmes, Abraham, Lacouture, Courtright, Paxman, Rude, Hilsenbeck, C. K. Osborne, Rimawi.
Statistical analysis: Wang, Hilsenbeck.
Obtained funding: Nangia, C. K. Osborne.
Administrative, technical, or material support: Niravath, Otte, Paxman, Rude, C. K. Osborne.
Supervision: Nangia, Papish, Holmes, Abraham, Lacouture, C. K. Osborne, Rimawi.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Niravath reported serving as a consultant for Novartis. Dr Holmes reported serving as a consultant to Genomic Health and Novartis. Dr Abraham reported serving as a speaker and consultant to Roche, Genentech, and Pfizer. Dr Lacouture reported receiving personal fees from Quintiles, Boehringer Ingelheim, AstraZeneca, Genentech, Foamix, Infinity Pharmaceuticals, Janssen Research and Development, and Novartis; and receiving research funding from Berg and Bristol-Myers Squibb. Mr Paxman reported serving as the CEO of Paxman Coolers Ltd, which sponsored the study and provided funding and equipment. Dr C. K. Osborne reported serving on advisory boards for AstraZeneca, Roche, Genentech, and PerkinElmer; and serving as a consultant for O'Melveny and Myers.

Funding/Support: This work was supported by Paxman Coolers Ltd, which contracted with Baylor College of Medicine to conduct the study. Dr Lacouture is supported in part by grant P30 CA008748 from the National Cancer Institute.

Role of the Funder/Sponsor: Paxman Coolers Ltd contributed to the design of the study relating to use of the scalp cooling device. Specifically, Paxman Coolers Ltd standardized the precooling and postcooling times of device use based on experience with the device and specific chemotherapy regimens. Paxman Coolers Ltd also trained all the sites on device use and proper cap fitting. Paxman Coolers Ltd had no role in the collection, management, analysis, or interpretation of the data. Paxman Coolers Ltd did not prepare any portion of the manuscript. Paxman Coolers Ltd did agree with submitting the manuscript for publication and reviewed and approved the initial manuscript prior to submission with no recommended changes, but could not prohibit publication of the results. The National Cancer Institute had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: We thank the women who participated in this study and thank the patients for granting permission to publish this information.

REFERENCES

1. Zdenkowski N, Tesson S, Lombard J, et al. Supportive care of women with breast cancer: key concerns and practical solutions. *Med J Aust*. 2016;205(10):471-475.

2. Trusson D, Pilnick A. The role of hair loss in cancer identity: perceptions of chemotherapy-induced alopecia among women treated for early-stage breast cancer or ductal carcinoma in situ [published online April 11, 2016]. *Cancer Nurs*. 2016. doi:10.1097/NCC.0000000000000373

3. van den Hurk CJ. *Safety and Effectiveness of Scalp Cooling in Cancer Patients Undergoing Cytotoxic Treatment*. Leiden, the Netherlands: Gildeprint Drukkerijen; 2013.

4. Massey CS. A multicentre study to determine the efficacy and patient acceptability of the Paxman Scalp Cooler to prevent hair loss in patients receiving chemotherapy. *Eur J Oncol Nurs*. 2004;8(2):121-130.

5. Lemieux J, Desbiens C, Hogue JC. Breast cancer scalp metastasis as first metastatic site after scalp cooling: two cases of occurrence after 7- and 9-year follow-up. *Breast Cancer Res Treat*. 2011;128(2):563-566.

6. van de Sande MA, van den Hurk CJ, Breed WP, Nortier JW. Allow scalp cooling during adjuvant chemotherapy in patients with breast cancer; scalp metastases rarely occur [in Dutch]. *Ned Tijdschr Geneeskd*. 2010;154:A2134.

7. Lemieux J, Amireault C, Provencher L, Maunsell E. Incidence of scalp metastases in breast cancer: a retrospective cohort study in women who were offered scalp cooling. *Breast Cancer Res Treat*. 2009;118(3):547-552.

8. Christodoulou C, Tsakalos G, Galani E, Skarlos DV. Scalp metastases and scalp cooling for chemotherapy-induced alopecia prevention. *Ann Oncol*. 2006;17(2):350.

9. van den Hurk CJ, van de Poll-Franse LV, Breed WP, Coebergh JW, Nortier JW. Scalp cooling to prevent alopecia after chemotherapy can be considered safe in patients with breast cancer. *Breast*. 2013;22(5):1001-1004.

10. Sneeuw KC, Aaronson NK, Yarnold JR, et al. Cosmetic and functional outcomes of breast conserving treatment for early stage breast cancer, 2: relationship with psychosocial functioning. *Radiother Oncol*. 1992;25(3):160-166.

Copyright 2017 American Medical Association. All rights reserved.

Downloaded From: on 01/18/2018

11. Münstedt K, Manthey N, Sachsse S, Vahrson H. Changes in self-concept and body image during alopecia induced cancer chemotherapy. *Support Care Cancer*. 1997;5(2):139-143.

12. van den Hurk CJ, Mols F, Vingerhoets AJ, Breed WP. Impact of alopecia and scalp cooling on the well-being of breast cancer patients. *Psychooncology*. 2010;19(7):701-709.

13. Pozo-Kaderman C, Kaderman RA, Toonkel R. The psychosocial aspects of breast cancer. *Nurse Pract Forum*. 1999;10(3):165-174.

14. Kornblith AB. Psychosocial adaptation of cancer survivors. In: Holland JC, Breitbart W, Jacobsen PB, et al, eds. *Psycho-Oncology*. Oxford, England: Oxford University Press; 1998:223-254.

15. Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A; EORTC Quality of Life Group. *The EORTC QLQ-C30 Scoring Manual*. 3rd ed. Brussels, Belgium: European Organisation for Research & Treatment of Cancer; 2001.

16. GL Assessment. Hospital Anxiety and Depression Scale (HADS). http://www.gl-assessment.co.uk/products/hospital-anxiety-and-depression-scale/hospital-anxiety-and-depression-scale-faqs. Accessed November 10, 2016.

17. Hopwood P, Fletcher I, Lee A, Al Ghazal S. A body image scale for use with cancer patients. *Eur J Cancer*. 2001;37(2):189-197.

18. Shin H, Jo SJ, Kim DH, Kwon O, Myung SK. Efficacy of interventions for prevention of chemotherapy-induced alopecia: a systematic review and meta-analysis. *Int J Cancer*. 2015;136(5):E442-E454.

19. Mols F, van den Hurk CJ, Vingerhoets AJ, Breed WP. Scalp cooling to prevent chemotherapy-induced hair loss: practical and clinical considerations. *Support Care Cancer*. 2009;17(2):181-189.

20. van den Hurk C, Peerbooms M, Komen M, Nortier H, Breed W. Multicenter results of scalp cooling to prevent chemotherapy-induced alopecia in 1500 breast cancer patients. Poster presented at: 34th Annual CTRC-AACR San Antonio Breast Cancer Symposium; December 6-10, 2011; San Antonio, TX.

21. van den Hurk CJ, Peerbooms M, van de Poll-Franse LV, Nortier JW, Coebergh JW, Breed WP. Scalp cooling for hair preservation and associated characteristics in 1411 chemotherapy patients—results of the Dutch Scalp Cooling Registry. *Acta Oncol*. 2012;51(4):497-504.

22. Edelstyn GA, MacDonald M, MacRae KD. Doxorubicin-induced hair loss and possible modification by scalp cooling. *Lancet*. 1977;2(8031):253-254.

23. Giaccone G, Di Giulio F, Morandini MP, Calciati A. Scalp hypothermia in the prevention of doxorubicin-induced hair loss. *Cancer Nurs*. 1988;11(3):170-173.

24. Ron IG, Kalmus Y, Kalmus Z, Inbar M, Chaitchik S. Scalp cooling in the prevention of alopecia in patients receiving depilating chemotherapy. *Support Care Cancer*. 1997;5(2):136-138.

25. Macduff C, Mackenzie T, Hutcheon A, Melville L, Archibald H. The effectiveness of scalp cooling in preventing alopecia for patients receiving epirubicin and docetaxel. *Eur J Cancer Care (Engl)*. 2003;12(2):154-161.

26. Satterwhite B, Zimm S. The use of scalp hypothermia in the prevention of doxorubicin-induced hair loss. *Cancer*. 1984;54(1):34-37.

27. Kennedy M, Packard R, Grant M, Padilla G, Presant C, Chillar R. The effects of using Chemocap on occurrence of chemotherapy-induced alopecia. *Oncol Nurs Forum*. 1983;10(1):19-24.

28. Parker R. The effectiveness of scalp hypothermia in preventing cyclophosphamide-induced alopecia. *Oncol Nurs Forum*. 1987;14(6):49-53.

29. Spaeth D, Luporsi E, Weber B, et al. Efficacy and safety of cooling helmets (CH) for the prevention of chemotherapy-induced alopecia (CIA): a prospective study of 911 patients (pts). *J Clin Oncol*. 2008;26(15S):9564.

30. Breed WPM, van den Hurk CJG, Peerbooms M. Presentation, impact and prevention of chemotherapy-induced hair loss: scalp cooling potentials and limitations. *Expert Rev Dermatol*. 2011;6(1):109-125. doi:10.1586/edm.10.76

31. Rugo HS, Klein P, Melin SA, et al. Clinical performance of the DigniCap system, a scalp hypothermia system, in preventing chemotherapy-induced alopecia. Poster presented at: 2015 ASCO Annual Meeting; May 29, 2015; Chicago, IL. Abstract 9518.

32. Komen MM, Smorenburg CH, van den Hurk CJ, Nortier JW. Factors influencing the effectiveness of scalp cooling in the prevention of chemotherapy-induced alopecia. *Oncologist*. 2013;18(7):885-891.

33. Lemieux J, Maunsell E, Provencher L. Chemotherapy-induced alopecia and effects on quality of life among women with breast cancer: a literature review. *Psychooncology*. 2008;17(4):317-328.

Copyright 2017 American Medical Association. All rights reserved.

Downloaded From: on 01/18/2018