ORIGINAL ARTICLE ◄

Scalp cooler efficacy to reduce anthracycline-induced alopecia and its psycho-social impact in breast cancer patients

Yousri Rostom, MD; Gamal El-Husseiny, MD; Anwar Salama, MD; Rasha El-Saka, MD

Clinical Oncology and Nuclear Medicine Department, Alexandria University, Egypt.

✉ *Corresponding Author: Dr Yousri Rostom, MD*
E-mail: rostomy@hotmail.com

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Background: Hair loss is one of the most common side effects of chemotherapy that is unavoidable and emotionally distressing. So, this study was carried out to evaluate the efficacy of scalp cooling in prevention or reduction of anthracyline-induced hair loss and its psychological impact in female breast cancer patients.
METHODS: The study included 120 female patients with breast cancer, treated in adjuvant setting, using anthracyline-based regimens. The patients were divided randomly into two equal groups: scalp cooling group (group I) in which patients received chemotherapy were subjected to scalp cooling and control group (group II) in which patients received chemotherapy without being offered scalp cooling. Hair loss was evaluated in all patients using WHO grading system at each cycle of chemotherapy. Quality of life was assessed using EORTC QLQ-C30 and EORTC QLQ-BR23.
Results: Eighty five percent of patients in scalp cooling group experienced grade 4 hair loss compared to 100% of patients in the control group after completing six cycles of chemotherapy. Only nine out of 60 patients (15%) in the scalp cooling group developed grade 1-2 hair loss and were considered as success. No significant relation was found between the degree of hair loss and the patient's age or the level of liver function tests. The scores of overall global health status and functional scales showed no significant difference between the two treatment groups except for scores on emotional functioning scale, body image and upset by hair loss.
Conclusion: Efficacy of scalp cooling remains doubtful. Chemotherapy-induced hair loss is stressful to the majority of patients. It affects various aspects of patient's life, especially emotional functioning and body image. More large randomized studies are needed to establish the benefit of scalp cooling and to explore other modalities for prevention of hair loss.

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Introduction

In spite of being temporary ; chemotherapy-induced hair loss is an extremely traumatic experience. It has profound psychosocial and quality of life consequences that include anxiety, depression, negative body image, lowered self-esteem and reduced sense of well-being. Alopecia increases one's identity as a cancer patient and the start of hair loss is an important moment in becoming aware of the cancer. [1] Occasionally alopecia can even generate sufficient anxiety for some patients to consider rejection of potentially curative treatment. [2]

Chemotherapeutic drugs attack rapidly dividing cells which may be malignant or normal. At any time, around 85–90% of human hair follicles are in a state of rapid growth. [3] Chemotherapy-induced alopecia occurs within 2 to 3 weeks of chemotherapy treatment. Alopecia normally resolves within 2 to 3 months after cessation of chemotherapy. When hair grows back, it may be of a different texture or color. The pathobiology of the response of human hair follicle to chemotherapy remains largely unknown. Cece et al. showed that doxorubicin affects proliferation in the hair follicle matrix cells and induces apoptosis followed by hair loss. [4,5] There are many factors affecting the severity of hair loss. They include the type of chemotherapy, the route, dosage and schedule of administration: High dose, intermittent, intravenous therapy is associated with a high incidence of complete alopecia. Low dose therapy, oral administration or weekly regimens are less likely to induce complete alopecia. Combination chemotherapy regimens are more likely to result in alopecia than are single agents. [3]

Measures to reduce or eliminate alopecia during chemotherapy have been investigated since the 1960s with varying degrees of success. They include tourniquets, scalp cooling systems and use of biological agents e.g. AS101, Inhibitors of CDK2, topical calcitriol. [6]

There are two scientific rationales for scalp cooling. The first is vasoconstriction. The second and the more important rationale is reduced biochemical activity, which makes hair follicles less susceptible to the damage of chemotherapeutic agents. [7] Few studies have been made to find out which method of scalp cooling is the most effective. Careful application of the cooling cap might be more important than the cooling system itself. [8]

Unfortunately, most studies on scalp cooling are small and of poor value. There are seven randomized clinical studies that involved a total of 233 patients. The success rate is relatively low in some of them with 10%, 25% and 37% of the patients considered to have good hair preservation in three studies. [9]

There are significant concerns of possible scalp recurrences as a result of using the scalp cooling system during chemotherapy. There is currently no clinical or

scientific evidence that the incidence of scalp metastases is increased in scalp cooled adjuvant breast cancer patients. Scalp cooling is not recommended for use in those tumors with a high prevalence of scalp metastasis or in patients with extensive haematological malignancies as cooling might prevent the effect of chemotherapy on tumor cells in the scalp skin. [10]

This work aims at evaluating the efficacy of Paxman scalp cooler to reduce anthracycline-induced alopecia and its psychosocial impact in female breast cancer patients.

Patients & Methods

The current study was conducted between July 2007 and August 2008. The study included 120 female patients with breast cancer, treated in adjuvant setting. These patients were chosen according to certain **inclusion criteria** (age ≤ 70 years, WHO performance status 0-1, adequate bone marrow, liver functions and renal functions and no evidence of metastatic disease) and **exclusion criteria** (active cardiac disease, significant arrhythmias, any serious medical or psychiatric conditions, other malignancy and previous breast cancer). The patients were divided randomly into two equal groups: scalp cooling group (group I) in which patients received chemotherapy with scalp cooling and control group (group II) in which patients received chemotherapy without being offered scalp cooling. The chemotherapeutic regimen consisted of doxorubicin (50 mg/m^2), 5-flurouracil (500 mg/m^2) and cyclophosphamide (500 mg/m^2) for six cycles, three weeks apart. Scalp cooling in group I patients was performed using Paxman Scalp Cooler. A pre-infusion cooling time of 20 minutes was done and the cap remained on the scalp during the infusion period (60-90 minutes) and two hours post-infusion. Hair loss was evaluated in all patients using WHO grading system at each cycle of chemotherapy and 3 WEEKS after the last cycle of chemotherapy with the reference to the control group. Quality of life was assessed using EORTC QLQ-C30 and EORTC QLQ-BR23. [11]

Results

The patient characteristics were homogenous between the two study groups with no statistically significant difference, except for age. (Table I)

Table 1: Patient and tumor characteristics of the studied 120 patients.

	Scalp cooling group		Control group		Total	
	No.	%	No.	%	No.	%
Age						
<50 years	35	58.3	32	53.3	67	55.8
>50 years	25	41.7	28	46.7	53	44.2
P value	0.024					
Menstrual status						
Postmenopausal	23	38.3	24	40	47	39.2
Premenopausal	37	61.7	36	60	73	60.8
P value	0.61					
Tumor Size						
T1	16	26.7	8	13.3	24	20
T2	32	53.3	34	56.7	66	55
T3	9	15	17	28.3	26	21.7
T4	3	5	1	1.7	4	3.3
p value	0.29					
Lymph Nodes						
No	25	41.7	16	26.7	41	34.2
N1	16	26.7	16	26.7	32	26.7
N2	12	20	18	30	30	25
N3	7	11.6	10	16.6	17	14.2
p value	0.31					

Eighty five percent of patients in scalp cooling group experienced grade 4 hair loss compared to 100% of patients in the control group after completing six cycles of chemotherapy. Only nine out of 60 patients (15%) in the scalp cooling group developed grade 1-2 hair loss and were considered success. When the data were examined cycle by cycle, it appeared that the incidence of grade 3-4 hair loss was lower in the scalp cooling group than in the control group following every cycle of chemotherapy. The difference was statistically significant except for cycle I. The incidence of grade 4 alopecia increased markedly after third cycle of chemotherapy in scalp cooling group (0% after cycle I, 3.3% after cycle II, 31.7% after cycle III and 61.7% after cycle IV). (Table II) These data suggest that scalp cooling may be more effective in patients receiving smaller number of chemotherapy cycles e.g. AC regimen. No significant relation was found between the degree of hair loss and the age of the patients and also the level of liver function tests. (Table III)

Table 2: Incidence of hair loss after cycle I-VI

Hair loss	Scalp cooling Group		Control Group	
	No.	%	No.	%
Cycle I				
Grade 0	15	25	6	10
Grade 1	8	13.3	11	18.3
Grade 2	24	40	24	40
Grade 3	13	21.7	19	31.7
Grade 4	0	0	0	0
p value	0.141			
Cycle II				
Grade 0	7	11.7	1	1.7
Grade 1	8	13.3	4	6.7
Grade 2	16	26.7	9	15
Grade 3	27	45	40	66.7
Grade 4	2	3.3	6	10
p value	0.015			
Cycle III				
Grade 0	7	11.7	0	0
Grade 1	2	3.3	3	5
Grade 2	7	11.7	2	3.3
Grade 3	25	41.7	22	36.7
Grade 4	19	31.7	33	55
p value	0.007			

Cycle IV				
Grade 0	4	6.7	0	0
Grade 1	4	6.7	0	0
Grade 2	1	1.7	2	3.3
Grade 3	14	23.3	9	15
Grade 4	37	61.7	49	81.7
p value	0.026			
Cycle V				
Grade 0	1	1.7	0	0
Grade 1	6	10	0	0
Grade 2	2	3.3	0	0
Grade 3	1	1.7	2	3.3
Grade 4	50	83.3	58	96.7
p value	0.042			
Cycle VI				
Grade 0	0	0	0	0
Grade 1	6	10	0	0
Grade 2	3	5	0	0
Grade 3	0	0	0	0
Grade 4	51	85	60	60
p value	0.008			

WHO grading system of hair loss: Grade 0: No significant hair loss, **Grade 1**: Minor hair loss, not requiring a wig, **Grade 2** :Moderate hair loss but not requiring a wig, **Grade 3** :Severe hair loss requiring a wig, **Grade 4** :Total alopecia. [12]

Table 3: Relation between age and hair loss after last cycle in the two study groups.

Grade of alopecia after the last cycle	Age						
	N	**Min**	**Max**	**Mean**	**S.D.**	**F**	**Sig.**
Grade 1	6	34	50	42.33	6.772	1.276	0.283
Grade 2	3	42	57	51.33	8.144		
Grade 4	111	29	70	47.94	9.377		
Grade of alopecia after the last cycle	**Total serum bilirubin (mg/dL)**						
	N	**Min.**	**Max.**	**Mean**	**S.D.**	**F**	**Sig.**
Grade 1	6	0.2	0.7	0.39	0.223	0.808	0.448
Grade 2	3	0.35	0.6	0.45	0.132		
Grade 4	111	0.2	0.96	0.494	0.202		
Grade of alopecia after the last cycle	**AST (U/L)***						
	N	**Min.**	**Max.**	**Mean**	**S.D.**	**F**	**Sig.**
Grade 1	6	19	49	31.16	11.12	0.405	0.668
Grade 2	3	20	30	23.33	5.773		
Grade 4	111	7	78	27.97	12.596		
Grade of alopecia after the last cycle	**ALT (U/L)***						
	N	**Min.**	**Max.**	**Mean**	**S.D.**	**F**	**Sig.**
Grade 1	6	31	58	41.33	9.791	0.288	0.751
Grade 2	3	22	47	32.00	13.228		
Grade 4	111	8	102	37.97	17.763		

*Normal value was up to 40U/L for AST and up to 45U/L for ALT

All patients were assessed for chemotherapy toxicity according to WHO toxicity criteria. The overall therapy was tolerated (Table IV). Eight patients (13.3%) in control group developed transient elevation of LFTs (grade 1-3) compared to only one patient in scalp cooling group (p = 0.06). Seventy-five percent of patients in scalp cooling group and 46.7% of control group developed grade 1 anemia, while 8.3% of patients in scalp cooling group and 30% of control group developed grade 2 anemia (p = 0.003). Grade 1 neutropenia was encountered in 27 patients (45%) and 42 patients (70%) from scalp cooling group and control group respectively. There was only one patient in each group developed grade 2 neutropenia (p = 0.039).

Table 4: Comparison between the two treated groups regarding non-hematological toxicity of chemotherapy.

Side effect	Scalp cooling Group		Control Group		Total	
	No.	**%**	**No.**	**%**	**No.**	**%**
Nausea						
Grade 0	0	0	1	1.7	1	0.8
Grade 1	39	65	31	51.7	70	58.3
Grade 2	21	35	28	46.7	49	40.8
p value	0.233					
Vomiting						
Grade 0	8	13.3	9	15	17	14.2
Grade 1	32	53.3	28	46.7	60	50
Grade 2	20	33.3	23	38.3	43	35.8
p value	0.765					
Nail changes						
Grade 0	6	10.0	8	13.3	14	11.7
Grade 1	54	90.0	52	86.7	106	88.3
p value	0.57					
Transaminases						
Grade 0	59	98.3	52	86.7	111	92.5
Grade 1	0	0	5	8.3	5	4.2
Grade 2	0	0	2	3.3	2	1.7
Grade 3	1	1.7	1	1.7	2	1.7
p value	0.06					
Anemia grade						
No anemia	10	16.7	14	23.3	24	20
Grade 1	45	75	28	46.7	73	60.8
Grade 2	5	8.3	18	30	23	19.2
p value	0.003					
Neutropenia						
No neutropenia	31	51.7	17	28.3	48	40
Grade 1	27	45	42	70	69	57.5
Grade 2	1	1.7	1	1.7	2	1.7
Grade 3	1	1.7	0	0	1	0.8
p value	0.039					

The side effects of scalp cooling were transient including sense of coldness and headache. Forty-four out of 60 patients (73.3%) showed acceptable degree of comfort throughout the cooling period.

The scores of overall global health status and functional scales showed no significant difference between the two treatment groups except for scores on

emotional functioning scale, body image and upset by hair loss. (Table V-VII) In the 111 patients who had hair loss 79 (71.2%) showed severe disturbance of emotional functioning, while in hair preservation group (9 patients): seven patients (77.8%) developed moderate disturbance and two patients (22.2%) had mild disturbance of emotional functioning (p=0.0001). In the hair loss group, 54.1% of the patients experienced moderate disturbance in body image. All patients in hair preservation group had mild disturbance in the body image.

Table 5: The global health status and functional scales in the two studied groups.

Functional Scale	Scalp cooling group		Control group		Total «n=120»	
	No.	%	No.	%	No.	%
Global health status /QOL						
Severe disturbance	7	11.7	8	13.3	15	12.5
Moderate disturbance	40	66.7	42	70	82	68.3
Mild disturbance	13	21.7	10	16.7	23	19.2
p value	0.77					
Physical functioning						
Moderate disturbance	18	30	22	36.7	40	33.3
Mild disturbance	42	70	38	63.3	80	66.7
p value	0.439					
Role functioning						
Severe disturbance	31	51.7	30	50	61	50.8
Moderate disturbance	22	36.7	26	43.3	48	40
Mild disturbance	7	11.7	4	6.7	11	9.2
p value	0.55					
Cognitive functioning						
Moderate disturbance	8	13.3	9	15	17	14.2
Mild disturbance	52	86.7	51	85	103	85.8
p value	0.99					
Social Functioning						
Severe disturbance	2	22.2	25	22.5	27	22.5
Moderate disturbance	1	11.1	38	34.2	39	32.5
Mild disturbance	6	66.7	48	43.2	54	45
X^2 P	2.45 0.653					

Table 6: Emotional functioning in the hair preservation and the hair loss groups.

Emotional functioning	Hair preservation Group		Hair loss Group		Total	
	No.	%	No.	%	No.	%
Severe disturbance	0	0	79	71.2	79	65.8
Moderate disturbance	7	77.8	20	18	27	22.5
Mild disturbance	2	22.2	12	10.8	14	11.7
X^2 P	20.82 0.0001					

Table 7: Body image disturbance in the two study groups.

Body image	Hair preservation Group		Hair loss Group		Total	
	No	%	No	%	No	%
Severe disturbance	0	0	51	45,9%	51	42.5
Moderate disturbance	0	0	60	54.1	60	50
Mild disturbance	9	100	0	0	9	7.5
X^2 p value	120.93 0.00001					

Discussion

In the present study, the success rate of scalp cooling was only 15%. In agreement with our study, Tollenaar et al. evaluated the effectiveness of scalp hypothermia in the prevention of alopecia caused by similar adjuvant chemotherapy in 35 patients with breast cancer. Only four patients (11%) showed acceptable hair preservation (no or minor alopecia), 12 patients (34%) had moderate alopecia, all requiring a wig and 19 patients (54%) had complete alopecia. [13] In another study, scalp hypothermia was used in 60 patients with breast cancer receiving chemotherapy with IV doxorubicin (40 mg/m2) and vincristine (1.4 mg/m2) on day 1 together with oral cyclophosphamide (200 mg/m2) on days 2-5. No patients retained enough hair to encourage them to continue scalp hypothermia throughout chemotherapy. All patients were rated as having poor hair retention. [14]

The successful effect of scalp cooling in the present study is less than that reported in some other studies inspite of using the standard doses of chemotherapy. A non-randomized study involved 94 patients with breast cancer, treated in the adjuvant or palliative setting. Most patients received regimen at doses of epirubicin ranging from 60 to 75 mg/m^2. Doxorubicin regimens as single agent or in combination were administered to 11 patients (12%) at doses ranging from 30 to 60 mg/m^2. The mean number of cycles given was not reported. Use of the Paxman Scalp Cooler was associated with a success for 89% of all patients and for 87% of patients who received FEC regimen. [15] In another study, breast cancer patients were treated with (n=98) or without (n=168) scalp cooling. Patients received one of the following intravenous adjuvant chemotherapies: AC; FEC; FAC and TAC. Scalp cooling was effective in preventing chemotherapy-induced hair loss in 32 of 62 available patients (52%). Scalp cooling was a burden for only 17 out of 51 patients (33%). The exact technique of scalp cooling was not described in this study. [16]

It is important to consider that all the patient in the present study received doxorubicin dose of 50 mg/m^2 in combination with cyclophsphamide (500mg/m^2) and 5-FU(500mg/m^2) for a total of six cycles which may partly explain the relatively low success rate in the present study. In general the degree of chemotherapy-induced alopecia is drug and dose dependent. Doxorubicin given as a single drug produces alopecia in 85-100% of patients, and an almost similar percentage of 75-90% alopecia is observed with intravenous cyclophosphamide. Scalp hypothermia resulted in minor or no hair loss in 66% of the patients when treated with doxorubicin ≤50 mg per injection. When 50-70 mg per injection was used, only 52% of the patients showed minor or no hair loss. When doxorubicin

dose was ≥70 mg per injection, the success rate was reduced to 44%. [13] Regimens with the highest incidence of alopecia included the combination of doxorubicin and cyclophosphamide, with complete alopecia in up to 96% of cases. [17] In the present study, the Incidence of complete alopecia in the control group is higher than that reported in other studies. This may be due to individual variations or genetic factors in the Egyptian population.

Also, in most studies the scale of the National Cancer Institute Common Toxicity Criteria was used. It is one of the simplest scales which grades alopecia as grade 0 (absent), grade 1 (mild) or grade 2 (severe). [18] Furthermore, our success rate of scalp cooling was defined after the completion of six cycles of chemotherapy. It is possible that success of scalp cooling in other studies was measured earlier and not always at the end of all cycles. This could also cause a difference in success rates between other studies and our study. Another possible explanation for our rather low success rate is publication bias. It is possible that studies having achieved low success rates have not been published after 1995. Furthermore, the sample of scalp-cooled patients was relatively small, which made subanalys less powerful. Also, longer follow-up is needed to evaluate the incidence of scalp metastasis in both study groups. Nevertheless, the results of the present study form an important contribution to the limited information available on scalp cooling to prevent chemotherapy-induced hair loss in cancer patients.

In the present work, patients in hair preservation group developed fewer disturbances in emotional functioning and body image, compared to patients in hair loss group. This is matched with the results of many other studies. A study was conducted to evaluate changes in body image during chemotherapy among 136 women with gynecologic malignancies who experienced alopecia. Results showed that chemotherapy-induced alopecia had an adverse effect on body image. [19] In another study, breast cancer patients were treated with or without scalp cooling. Even though patients knew hair loss was temporary, it was a burden to 54% of them. Patients were moderately satisfied with the re-growth of their hair after chemotherapy. Successfully cooled patients rated their hair as less important for their body image compared to patients who did experience hair loss (p=0.014). [16]

There are still many questions to be answered in the practice of scalp cooling. This may be due to the rather short history of supportive care, the underestimation of the impact of temporary hair loss on patients, the small number of studies in which the biochemical and biophysical processes playing a role in the hair loss have been investigated and possibly also the difficulties of clinical trials in these areas. There are fewer than 100 reports of scalp cooling for the prevention of chemotherapy-induced hair loss. They often contain merely one method of scalp cooling in a limited number of patients, regularly without control patients. The progress in the understanding and prevention of chemotherapy-induced hair loss is small and insignificant. It is hoped that more randomized trials will be conducted to optimize the use of scalp cooling and other methods to minimize chemotherapy-induced hair loss.

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