The efficacy and tolerability of scalp cooling in preventing chemotherapy-induced alopecia in patients with breast cancer receiving anthracyline and taxane-based chemotherapy in an Asian setting

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Abstract

BACKGROUND: Scalp cooling has been shown in several studies to be an effective method in preventing chemotherapy-induced alopecia (CIA). Data on the use of scalp cooling in Asian countries are limited, and evidence for its use and efficacy among our patients are not available.

OBJECTIVE: The aim of this study was to assess the effectiveness and tolerability of scalp cooling among breast cancer patients in our study population.

METHODS: Consecutive breast cancer patients receiving FE₇₅C, FE₁₀₀C, FE₁₀₀C-D, docetaxel₁₀₀ or docetaxel, and cyclophosphamide (TC) at our treatment center were recruited and allocated to the treatment (scalp cooling, DigniCap™ system) or control group in this prospective nonrandomized controlled study. The assessment of alopecia was carried out using the World Health Organization grading system and clinical photographs.

RESULTS: Seventy patients were recruited, but only 25 completed the study and were evaluable for analysis. Five of 12 patients (42%) in the scalp cooling group managed to preserve hair. Two of three patients who received FE₁₀₀C and TC regimens had minimal hair loss. All patients treated with FE₁₀₀C had severe hair loss. Half of all patients who received scalp cooling throughout chemotherapy rated the treatment as reasonably well tolerated. The most common reason for discontinuing scalp cooling was intolerance to its side effects.

CONCLUSION: Scalp cooling is potentially effective in reducing CIA caused by docetaxel, TC, and FE₁₀₀C chemotherapy regimen. However, it was not well tolerated by our study population. The dropout rate was high, and this needs to be taken into consideration when pursuing further trials in a similar setting.

Key Words: Anthracycline, chemotherapy-induced alopecia, cold-cap, docetaxel, scalp cooling

Introduction

Chemotherapy-induced alopecia (CIA) or hair loss is a common side effect of chemotherapy, but it is often given less attention compared to other side effects such as nausea, vomiting, bone marrow toxicity particularly neutropenia, lethargy, and mucositis. Many clinicians underestimate the impact of hair loss on patients. Although CIA is temporary and not life-threatening, it is one of the most feared side effects of cancer therapy and can be psychologically devastating.[1-3] There may be a negative influence on how the patients feel about themselves and their sexuality, leading to depression, loss of self-esteem, and a sense of helplessness.[1,2] It can be a reason for some patients to decline a potentially curative or life-prolonging treatment.

To date, scalp cooling is the best method to reduce CIA. Studies have shown promising results in patients who received scalp cooling.[3-6] Several techniques have been used to induce hypothermia: chilled air for cooling, simple bags with crushed ice, frozen cryogel packs or packs with endothermic cooling reaction for cooling the scalp, special caps with cryogel and an insulation layer, and caps connected to a cooling device using air or fluid as a medium and equipped with a thermostat.[7,8] It has been shown that scalp cooling can prevent hair loss caused by chemotherapy by diminishing intrafollicular metabolism and causing vasoconstriction of the blood vessels, thus reducing the amount of drug delivered to the hair follicles.[8,9] Despite its promising success rate, the number of hospitals offering this procedure is limited.[10,11] Scalp cooling as a method of preventing or reducing CIA is more widely used in European countries than in other parts of the world, particularly in Asian countries, where the usage is limited.[11,12] A literature search revealed very limited data on the effectiveness of scalp cooling among the Asian population, except for a recent Japanese report on this treatment.[13] DigniCap scalp cooling system was the first cooling cap that attained the United States Food and Drug Administration (FDA) approval in December 2015 for use in Stage I and II breast cancer patients receiving chemotherapy that may cause significant alopecia.[14] Since then, Paxman Scalp Cooling System has been FDA approved for the same application, and DigniCap was approved for CIA in other solid tumors.[14] We believe that clinicians and healthcare professionals need some data on the effectiveness of scalp cooling among the Asian population as many cancer patients in this region may benefit from the use of scalp cooling to prevent CIA.

This study describes the results of a prospective nonrandomized-controlled study conducted at a local teaching hospital using DigniCap scalp cooling system. The aim of this study was to evaluate the efficacy and tolerability of scalp cooling among breast cancer patients receiving chemotherapy with the risk of alopecia.

How to cite this article: Saad M, Chong FL, Bustam AZ, Ho GF, Malik RA, Ishak WZ, et al. The efficacy and tolerability of scalp cooling in preventing chemotherapy-induced alopecia in patients with breast cancer receiving anthracycline and taxane-based chemotherapy in an Asian setting. Indian J Cancer 2018;55:157-61.
Methods

Study design and sample
Seventy breast cancer patients who received anthracycline and taxane-based chemotherapy at the Clinical Oncology Unit at our medical center were recruited to this prospective nonrandomized controlled study between February and December 2010. Patients who took part in this study. The patients can fulfill the inclusion criteria but not the exclusion criteria. Inclusion criteria were as follows: (1) A confirmed breast cancer diagnosis; (2) Normal hair distribution at baseline; (3) Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, and (4) Having neoadjuvant, adjuvant, or metastatic chemotherapy. Exclusion criteria were as follows: (1) prior radiotherapy involving the head; (2) having inherent alopecia due to causes other than chemotherapy; (3) current or previous diagnosis of hematological malignancy; (4) having any condition where scalp cooling is contraindicated such as cold sensitivity, cold agglutinin disease, cryoglobulinemia and cryofibrinogenemia; and (5) Pregnant or breast-feeding. Patients were informed of the relatively rare risk of scalp metastasis with scalp cooling. Patients were given one of the following chemotherapeutic regimens: FE(75–100)C (5-fluorouracil 600 mg/m², cyclophosphamide 600 mg/m², FE(100)C-D (5-fluorouracil 500 mg/m², epirubicin 100 mg/m², cyclophosphamide 500 mg/m² followed by docetaxel 100 mg/m²), docetaxel 75 mg/m² or docetaxel and cyclophosphamide (TC) (docetaxel 60–75 mg/m², cyclophosphamide 600 mg/m²). All chemotherapy treatments were in 3-weekly schedules with each having a total number of six cycles (except for TC that required only four cycles). Patients who agreed for the scalp cooling treatment were enrolled into the scalp cooling group, whereas those who declined the intervention were enrolled to be in the control group. Scalp cooling was not an FDA-approved treatment at the time of the study. The study was performed to assess its feasibility in our patients as specified in the inclusion and exclusion criteria.

Ethical consideration
Written consent was obtained from all participating patients. This study was approved by the Medical Ethics Committee at our institute (MEC Ref: 714.17).

Measurements/instruments
Scalp cooling was achieved using the DigniCap™ system (Dignitana AB, Sweden). The system consists of a refrigerator unit and a control unit, integrated into a mobile cabinet, where two cooling caps are connected on each side. This allows two patients to be treated at the same time. The cap consists of two layers. The inner layer is made of silicone, and its smooth surface allows snug fitting and optimal contact between the cap and the patient’s scalp. The canals in the silicone cap are divided into two separate circuits, one for the forehead and one for the back of the head. Liquid coolant is pumped through the tubes, which run to the cap. The outer cap is made of neoprene that functions as an insulator. The system allows a gradual reduction from room temperature to the desired temperature. Deviations from the set temperature are detected and adjusted by the system. Scalp temperature can be controlled with an accuracy of ±2°C. Scalp cooling was initiated 30 min before administration of chemotherapy and was maintained at 5°C throughout the session and postchemotherapy. The duration of postchemotherapy cooling time differed according to the chemotherapy regimen used—60 min for FE75C, docetaxel, and TC; and 150 min for FE100C.

Data collection/assessment
Patients were assessed at baseline, before each chemotherapy cycle and at 6 weeks and 3 months after the completion of chemotherapy. Each assessment included grading and photographic documentation of alopecia, side effects from scalp cooling as well as patients’ tolerance and satisfaction level. Assessment of hair loss was carried out using clinical photographs and grading of alopecia according to the World Health Organization scale: grade 0, no hair loss; grade 1, minimal hair loss; grade 2, moderate hair loss; grade 3, reversible complete hair loss; and grade 4, irreversible complete hair loss.[15] Grade ≤2 is considered as satisfactory hair preservation whereas grade ≥3 is considered as significant alopecia. Patients’ satisfaction and tolerability were assessed using questionnaires. Only patients who completed all scalp cooling treatment and assessment procedures were eligible for analysis.

Data analysis
The difference in the success rate between the scalp cooling group and control group was analyzed using Fisher’s exact test. Statistical analysis was performed using the Stata/IC 11.0. P < 0.05 was considered statistically significant.

Results
A total of 70 patients with breast cancer were recruited for this study—44 in scalp cooling group and 26 in control group. Of these, only 25 patients were eligible for assessment—12 patients in the scalp cooling group and 13 patients in the control group. Forty-five patients were nonevaluable as they withdrew from the study before the completion of treatment and assessment. The reasons for withdrawal are outlined in Table 1.

The most common reason for discontinuing scalp cooling was intolerable side effects. The side effects reported were headaches and cold sensation in the scalp and vomiting. Of nine patients who had a headache, six stopped the treatment after the first cycle whereas the remaining three stopped after two cycles, the headache experienced rarely extended beyond one day. One patient who experienced scalp coldness discontinued the treatment after the first cycle, but another

| Table 1: Reasons for withdrawal from study in nonevaluable patients in both groups |
|---------------------------------|----------------|----------------|
| Reasons                        | Scalp cooling | Control        |
| (n=32), n (%)                  | (n=13), n (%) |
| Unable to tolerate side effects| 11 (34)       | 0              |
| Dissatisfaction with treatment/result | 8 (25)       | 0              |
| Logistical and technical problem| 7 (22)        | 3 (23)         |
| Others                         | 6 (19)        | 10 (77)        |
Seven patients were not satisfied with the results of scalp cooling. Of these, four had grade 1 alopecia at cycle two, one had grade 1 alopecia at cycle three, and two had grade two at cycles two and five, respectively. In addition, one patient was dissatisfied with the treatment due to the restriction of mobility during chemotherapy. Seven patients withdrew from the study due to logistical and technical issues. Of these, three felt that the treatment was too long, one felt it was inconvenient to come earlier and stay longer for scalp cooling treatment, two missed the scalp cooling treatment, and one did not have the treatment due to technical issues with the cooling system. The proper assessment could not be carried out after two patients had had their heads shaved whereas another four patients withdrew from the study without stating their reasons for doing so.

In the control group, eight patients had their heads shaved; three were uncomfortable with the assessment of hair loss, one switched to oral chemotherapy, and another defaulted chemotherapy.

Table 2 shows the frequency of alopecia assessed at mid-cycle (cycle 3) and at the last cycle (cycle 6), except for the TC regimen, which was analyzed at cycles two and four, respectively. There were no patients with grade 0 alopecia in either group during the evaluation of hair loss. At mid-cycle, the percentages of hair loss in both groups were almost similar. In the scalp cooling group, patients who managed to keep their hair at cycle two continued to do so at the last cycle, whereas all 13 patients in the control group had major hair loss or total alopecia at the last cycle. By employing Fisher’s exact test, the efficacy of the scalp cooling treatment at the last cycle showed a statistically significant result when compared to the control group ($P = 0.015$). A photographic example of a patient in the scalp cooling group with grade 1 alopecia at the first and last cycle of TC regimen is demonstrated in Figures 1 and 2, respectively.

Table 3 shows the efficacy of scalp cooling according to the different chemotherapy regimens. Protection against high-grade alopecia with scalp cooling treatment was observed in a patient who received docetaxel. In the scalp cooling group, two of three patients who received $\text{FE}_{75} \cdot \text{C}$ and TC regimens, respectively, had minimal hair loss (grade 1). However, all patients who were treated with $\text{FE}_{100} \cdot \text{C}$, alone or with docetaxel, had severe hair loss while on scalp cooling. A total of five patients were assessed as having minimal or moderate hair loss, and this translates into a success rate of 42% in patients who received the scalp cooling treatment.

When asked to assess their level of tolerability during the scalp cooling treatment, 6 of 12 patients felt that scalp cooling was very well tolerated, well tolerated, or reasonably tolerated. The same patients were asked if they were satisfied with the results and 75% satisfaction was reported. The full results are shown in Table 4.

Table 2: Frequency of alopecia during assessment at mid and last cycle of chemotherapy

<table>
<thead>
<tr>
<th></th>
<th>Scalp cooling ($n=12$), $n$ (%)</th>
<th>Control ($n=13$), $n$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mid cycle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopeia grade ≤2</td>
<td>5 (42)</td>
<td>6 (46)</td>
</tr>
<tr>
<td>Alopeia grade ≥3</td>
<td>7 (58)</td>
<td>7 (54)</td>
</tr>
<tr>
<td>Last cycle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopeia grade ≤2</td>
<td>5 (42)</td>
<td>0</td>
</tr>
<tr>
<td>Alopeia grade ≥3</td>
<td>7 (58)*</td>
<td>13 (100)</td>
</tr>
</tbody>
</table>

*Comparison of patients in the scalp cooling group with patients in the control group: $P<0.05$

Table 3: Efficacy of scalp cooling at the last cycle based on different chemotherapy regimens

<table>
<thead>
<tr>
<th>Chemotherapy regimen</th>
<th>Scalp cooling ($n=12$)</th>
<th>Control ($n=13$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of patients</td>
<td>Alopecia grade ≤2</td>
</tr>
<tr>
<td>$\text{FE}_{75} \cdot \text{C}$</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>$\text{FE}_{100} \cdot \text{C}$</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>$\text{FE}_{100} \cdot \text{C} \cdot \text{D}$</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>TC</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Docetaxel (75)</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

$\text{C}=\text{Cyclophosphamide}; \text{D}=\text{Docetaxel}; \text{E}=\text{Epirubicin}; \text{F}=5\text{-Fluorouracil}; \text{T}=\text{Taxane}$ (docetaxel)
Discussion

Since the 1970s, scalp cooling has been used as a method to prevent CIA. Tolerance to scalp cooling varied between different patient populations, ranging from complete intolerance leading to treatment withdrawal to a tolerance level that allows scalp cooling throughout all cycles of chemotherapy.

In our study population, scalp cooling was reasonably tolerated in only a small proportion of patients. Majority of patients withdrew from the study due to their inability to tolerate its side effects mainly headache and scalp coldness. Among these, the headache was the most common factor that led to the withdrawal of patients from the scalp cooling treatment. The findings of overall low patient acceptability and tolerance were in contrast with other literature where there were lower rates of withdrawal in patients who experienced side effects.

In our cohort of patients, scalp cooling was perceived as a burden by a handful of patients in the scalp cooling group, that seemed to have outweighed the burden of hair loss during chemotherapy. A number of patients stopped scalp cooling even when their alopecia grading was considered to be successful. The higher expectations of these patients might have led to the discontinuation of the scalp cooling treatment. The fact that they had to come earlier and stay later for the scalp cooling plus the attached wires needing to be disconnected and reconnected when they went to the toilet are inconveniences that some find unacceptable. For those who were wearing headscarves, the temporary hair loss might be something that they could bear with. A proportion of patients, especially in the control group, went ahead with shaving their hair early on during chemotherapy. This suggests that culturally temporary hair loss is more acceptable than we had expected in our study population.

There were no patients with grade 0 alopecia following commencement of chemotherapy and throughout the duration of treatment. This seems to suggest that scalp cooling did not help to prevent hair loss during chemotherapy but rather helped to reduce the severity of hair loss. This study produced a success rate of 42% with scalp cooling treatment and is considered as a moderate success rate based on a literature review by Breed et al., whereby the percentage of patients with good hair preservation varied between 0% and 100%. As most of these studies were conducted in Europe, it was difficult to make a direct comparison on patients’ tolerability, acceptability, and efficacy of scalp cooling. It has to be taken into account that our study was conducted in a multiracial Asian population where physiological response and tolerance to cold may differ from the European population. Furthermore, there has been consistent historical evidence that East Asian individuals are more susceptible to the effects of some chemotherapy agents than their Western counterparts. This may explain the lower success rate of scalp cooling in our study population as compared to most published reports that were conducted in European countries.

In addition, the use of more intensive chemotherapy could have contributed to the low success rate of scalp cooling in this study. Patients in the scalp cooling group who were treated with FE had more hair loss than those who received FE. This may imply that epirubicin at doses higher than 75 mg/m^2 may render the scalp cooling treatment ineffective, and this was also shown in several other studies that used similar chemotherapeutic regimens. When a combination of anthracycline and taxane was used, the result was less positive, with all patients reported having high-grade alopecia. The patient who received single agent taxane (docetaxel) achieved good hair preservation, which was in accordance with several other reports. The addition of cyclophosphamide to docetaxel showed a reduced success rate. Total protection was not achieved in this regimen, which may be explained by the different pharmacokinetic profile of cyclophosphamide.

One concern of using scalp cooling to prevent CIA is the possibility of an increased risk of developing scalp metastasis due to decreased chemotherapeutic drug perfusion in the scalp caused by reduced blood flow. Unfortunately, we did not follow-up for such end-point and occurrence. Although scalp metastasis is a concern, a recent systematic review and meta-analysis has found that scalp cooling did not increase the incidence of scalp metastasis. They have analysed scalp cooling publications with a total of 1989 patients over an estimated mean time frame of 43.1 months.

The number of patients eligible for analysis in our cohort for both the scalp cooling and control groups was small due to high dropout rates. However, these numbers were comparable to some of the previous studies. A higher number of evaluable patients are needed to confirm the efficacy and benefit of the scalp cooling treatment among our study population. Based on this study, overall 64% (73% in scalp cooling and 50% in control groups) dropout rate has to be taken into account in estimating the number of patients needed for future studies including measures to be taken to reduce this dropout rate.

Finally, our study included breast cancer patients from various stages including seven and four patients in the scalp cooling group with stages III and IV, respectively. However, the majority were from stages I and II. It is important to highlight that FDA approved scalp cooling in 2015 for early-stage breast cancer and 2017 for other solid tumors. Therefore, until we have more evidence for use in advanced breast cancer, its use should be limited according to approved indication.
Conclusion

Scalp cooling was not well tolerated in our study population. Nevertheless, it was fairly effective in reducing CIA with certain chemotherapy regimens in a proportion of patients who could persevere with the treatment.\textsuperscript{18,26}

Financial support and sponsorship

The study was supported by PJP Grant FS335/2008C from the Ministry of Higher Education of Malaysia. The DignicapTM scalp cooling system was sponsored by Dignitana AB, Sweden. Both sponsors have no involvement in study design, collection, analysis and interpretation of data, in the writing of the manuscript and in the decision to submit the manuscript for publication.

Conflicts of interest

There are no conflicts of interest.

References