Results of scalp cooling during anthracycline containing chemotherapy depend on scalp skin temperature

M.M.C. Komen a, *, C.H. Smorenburg b, J.W.R. Nortier c, T. van der Ploeg d, C.J.G. van den Hurk e, J.J.M. van der Hoeven f

a Department of Internal Medicine and Medical Oncology, Noordwest Ziekenhuisgroep, Wilhelminalaan 12, Alkmaar, 1815 JD, The Netherlands
b Department of Medical Oncology, Antoni van Leeuwenhoek, Plesmanlaan 121, Amsterdam, 1066 CX, The Netherlands
c Department of Medical Oncology, Leiden University Medical Centre, PO Box 9600, Leiden, 2300 RC, The Netherlands
d Science Department, Noordwest Ziekenhuisgroep, Wilhelminalaan 12, Alkmaar, 1815 JD, The Netherlands
e Comprehensive Cancer Organisation the Netherlands, PO Box 231, Eindhoven, 5600 AE, The Netherlands
f Department of Medical Oncology, Radboud University Medical Centre, Geert Grooteplein Zuid 10, 6525 GA, Nijmegen, The Netherlands

Article info

Article history:
Received 12 November 2015
Received in revised form 16 August 2016
Accepted 10 September 2016

Keywords:
Chemotherapy
Scalp cooling
Scalp temperature
Alopecia

Abstract

Objectives: The success of scalp cooling in preventing or reducing chemotherapy induced alopecia (CIA) is highly variable between patients undergoing similar chemotherapy regimens. A decrease of the scalp skin temperature seems to be an important factor, but data on the optimum temperature reached by scalp cooling to prevent CIA are lacking. This study investigated the relation between scalp skin temperature and its efficacy to prevent CIA.

Materials and methods: In this explorative study, scalp skin temperature was measured during scalp cooling in 62 breast cancer patients undergoing up to six cycles of anthracycline containing chemotherapy. Scalp skin temperature was measured by using two thermocouples at both temporal sides of the head. The primary end-point was the need for a wig or other head covering.

Results: Maximal cooling was reached after 45 min and was continued for 90 min after chemotherapy infusion. The scalp skin temperature after 45 min cooling varied from 10 °C to 3 °C, resulting in a mean scalp skin temperature of 19 °C (SEM: 0.4). Intrapersonal scalp skin temperatures during cooling were consistent for each chemotherapy cycle (ANOVA: P = 0.855). Thirteen out of 62 patients (21%) did not require a wig or other head covering. They appeared to have a significantly lower mean scalp skin temperature (18 °C; SEM: 0.7) compared to patients with alopecia (20 °C; SEM: 0.5) (P = 0.01).

Conclusion: The efficacy of scalp cooling during chemotherapy is temperature dependent. A precise cut-off point could not be detected, but the best results seem to be obtained when the scalp temperature decreases below 18 °C.

Trialregister.nl NTR number: 3082

© 2016 Elsevier Ltd. All rights reserved.

Introduction

Alopecia is a much feared side effect of chemotherapy and may have an impact on treatment decisions [1–6]. Scalp cooling still remains the only current intervention to prevent chemotherapy induced alopecia (CIA). It is assumed that scalp cooling works by inducing local vasoconstriction and reduction of metabolism of the administered cytostatic agents [7,8]. Vasoconstriction reduces the blood flow to the hair follicles in the period of peak plasma concentration of the relevant chemotherapeutic agent. Reduced metabolic activity makes hair follicles less vulnerable to the damage caused by chemotherapy. Although a decrease of the scalp skin temperature seems to be relevant for the results of cooling, data on the optimal temperature required for hair protection are scarce. There are suggestions in the literature that a subcutaneous scalp skin temperature below 22 °C [9] (corresponding to an epicutaneous scalp temperature below 19 °C [7]) is required for hair preservation, but considerable variations have been reported on
the desirable scalp temperature reached during scalp cooling [7,9–13]. Hillen et al. [11] attributed the success of their air-cooling method in part to achieving epicutaneous temperatures below 15 °C, whereas the average epicutaneous scalp temperature of three volunteers recorded in a study of Massey [13] was 16 °C. Al-Tameemi et al. [14] used in vitro models to provide evidence that temperature conditions may be critical in the efficacy of cooling by rescuing cells from drug-mediated toxicity. Although previous in vitro reports concluded that further cooling below 22 °C would not provide any further protection against doxorubicin-mediated keratinocyte cytotoxicity [15], it was shown that lowering the temperature from 22 °C to 18 °C and even further to 14 °C in human keratinocyte models resulted in a better degree of rescue from drug cytotoxicity. Based on the current available knowledge, it is not possible to draw conclusions on the optimal scalp temperature for effective cooling.

To investigate the relation between the obtained scalp skin temperature during scalp cooling and its outcome in preventing CIA, we measured scalp skin temperatures during the procedure of scalp cooling in breast cancer patients treated with anthracycline containing chemotherapy.

Materials and methods

We conducted an explorative single-centre study between August 2010 and January 2014 at the department of Internal Medicine of the Medical Centre Alkmaar, the Netherlands. The study enrolled patients with primary breast cancer who were planned for adjuvant chemotherapy with up to six cycles of 5-Fluorouracil-Epirubicin-Cyclophosphamide (FEC) or Adriamycin-Cyclophosphamide (AC) and who were willing to use scalp cooling to prevent CIA. The study was approved by an independent ethics committee and institution review board. All procedures were conducted in accordance with the 1964 Helsinki Declaration and its subsequent amendments. Written informed consent was obtained from all patients included in the study.

Inclusion criteria were primary invasive breast cancer without distant metastases. Patients had to be planned for treatment with three to six cycles FEC combination chemotherapy with an epirubicin dose of 90–100 mg/m² at 3-weekly intervals or with AC combination chemotherapy with doxorubicin at a dose of 60 mg/m². Subsequent chemotherapy cycles consisting of docetaxel monotherapy (100 mg/m²) were allowed after 3 FEC cycles. Patients were excluded if they lacked basic proficiency in Dutch, if they were unable to understand the patient information brochure or if they suffered from cold sensitivity, cold agglutinin disease, cryoglobulinemia, cryofibrinogenemia or cold posttraumatic dystrophy.

The one-person Paxman cooling machine (PSC-1) was used in this study. The temperature of the coolant in the refrigeration tank was −10 °C. This temperature is a standard set-up installed by the manufacturer. The cool cap was applied before cooling, with a pre-infusion cooling time of 45 min before the start of intravenous infusion of chemotherapy. Scalp cooling was continued during the administration of the chemotherapy with a post-infusion cooling time of 90 min after the end of chemotherapy infusion. Scalp cooling was applied in all planned cycles of chemotherapy, unless the patient decided to stop the cooling procedure because of hair loss, side effects or for patients’ preference.

At baseline, patient characteristics and objective hair quantity were collected. Objective hair quantity was measured with a Hair Check. The mechanical device compresses a bundle of hair in a disposable cartridge from a delineated area of the scalp and measures its cross-sectional area (Hair Mass Index, HMI). HMI incorporates both density and diameter and was measured at both temporal sides. Tolerance of scalp cooling was measured during all visits by a Visual Analogue Scale (VAS) of 0–10, in which 0 represented ‘not tolerable at all’ and 10 meant ‘very tolerable’. Patients were also asked whether they experienced other side effects such as headaches. The success of scalp cooling was defined in terms of the patient’s self-determined need to wear a wig or other head covering. Patients were considered evaluable for hair preservation if they were treated with at least three cycles of chemotherapy or if they discontinued scalp cooling due to severe hair loss. The epidermal temperature at the surface of the scalp was measured using two calibrated J type thermocouples that were fixed with medical glue at the left and right temporal side. To ensure that the registered temperature was a good measure for the skin temperature, each thermocouple end was modified with a specially developed aluminium disc with a diameter of 4 mm and a thickness of 0.5 mm. This facilitated the attachment to the scalp skin and, in combination with the medical glue, ensured that the thermal resistance between the thermocouple and the scalp skin was lower than the thermal resistance between the thermocouple and the cold cap. The temperature was measured continuously from the start until the end of the scalp cooling process.

Statistical analysis

Data were collected using standard forms, which were compiled into a SPSS database (SPSS version 20.0).

A paired t-test was used to check differences between the two measuring positions on the left and right temporal side. Differences in temperature between patients with and without head covering were analysed by the Mann–Whitney test. Repeated analysis of variance (ANOVA) was used for intergroup differences. All tests of significance were two-sided, and differences were considered statistically significant when \( P < 0.05 \). All tests were performed using SPSS software (version 20.0) for Windows XP.

Results

Patient characteristics

In this study a total of 62 female patients with breast cancer were included. Patient characteristics and the efficacy of scalp cooling are listed in Table 1. The median age of the patients was 60 years. The mean baseline HMI was 64 (range 24–101)

All patients were treated conform the protocol, with a median of 3 cycles of chemotherapy and scalp cooling. The median duration of scalp cooling was 195 min per cycle. All patients were evaluable for hair preservation and side effects. Four patients were not evaluable for temperature measurements because of probe dislocation or because probes came loose. At the time of data cut-off (January 1, 2014), the median follow-up of patients was 29 months.

Scalp temperature

Temperature measurements at the left and right temporal side of the head did not show significant differences. Scalp skin temperatures were therefore reported as the mean of the two measuring points. Maximal cooling was reached after 45 min and was continued for 90 min after chemotherapy infusion. The scalp skin temperature following 45 min cooling varied between patients from 10 °C to 31 °C, resulting in a mean scalp skin temperature of 19 °C (SEM: 0.4). However, in each individual patient, a consistent temperature was obtained on repeated measurement (ANOVA: \( P = 0.855 \) (Fig. 1).
Prevention of hair loss

The most pronounced hair loss was recorded after cycle 1: 40% of the patients lost their hair after the first treatment. Thirteen out of 62 patients (21%) showed satisfactory hair retention during anthracycline containing chemotherapy (Table 1). Although these patients suffered from slight hair loss, they did not feel the need to wear a wig or other head covering. The pattern of hair loss (global or patchy) was measured after every cycle of chemotherapy. 85% of the patients with global and 75% of the patients with patchy hair loss required a head covering. The baseline HMI score was not predictive for hair loss (HMI no head covering 61; HMI head covering 64; \( P = 0.7 \)) Fig. 2 and Table 2 show the mean scalp skin temperatures during scalp cooling for patients with and without head covering. Patients with good hair retention had a mean scalp skin temperature of 18 °C (SEM: 0.7) while patients with hair loss resulting in the use of a wig or other head covering had a mean scalp skin temperature of 20 °C (SEM: 0.5) (\( P = 0.01 \)) (Table 3). Because of the high variation in mean scalp skin temperatures in our patients, it was not possible to detect a threshold scalp skin temperature below which hair retention was always observed.

Toxicity and tolerance

Scalp cooling was very well tolerated. A VAS score for tolerance of scalp cooling was performed after 192 cooling procedures, resulting in a mean score of 8 (SD: 1.9). Only one patient stopped scalp cooling because of intolerance after cycle 4. Information about headaches was reported after 194 cooling procedures: in 163 sessions (84%) patients reported no headache; while headache was reported as minimal, moderate or severe in 23 (12%), 4 (2%) and 4...
(2%) sessions, respectively. Only fourteen percent of all patients in the study used paracetamol somewhere during their cycles to prevent headaches. No other side effects were reported (Table 4). No scalp metastases were reported during follow up.

**Discussion**

To our knowledge this is the first study measuring scalp skin temperature during scalp cooling with a Paxman scalp cooling machine to prevent CIA in patients treated with anthracycline containing chemotherapy. Maximal cooling was reached after 45 min and was continued for 90 min after chemotherapy infusion. Intrapersonal scalp skin temperatures during cooling were consistent for each chemotherapy cycle, but scalp skin temperatures were highly variable between patients, ranging from \(10^\circ C\) to \(31^\circ C\), resulting in a mean scalp skin temperature of \(19^\circ C\). Thirteen out of 62 patients (21%) did not require a wig or other head covering and showed satisfactory hair preservation. These patients appeared to have a significantly lower mean scalp skin temperature (\(18^\circ C\); SEM: 0.7) during cooling than patients with alopecia (\(20^\circ C\); SEM: 0.5) \((P = 0.01)\). The exact determinants on the efficacy of scalp cooling in the prevention of CIA are unknown [16–18]. Factors like the type and dose of chemotherapy can influence the outcome of scalp cooling [16]. Based on the results of this study, we can conclude that the temperature of the scalp skin is another important variable related to the efficacy of scalp cooling to prevent hair loss. Patients with good hair retention reached significant lower scalp skin

---

**Table 2**

Mean scalp skin temperatures in degrees Celsius during scalp cooling in all patients.

<table>
<thead>
<tr>
<th>Time (minutes)</th>
<th>No head covering</th>
<th>Head covering</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SEM</td>
<td>Mean</td>
</tr>
<tr>
<td>T = 0 (start scalp cooling)</td>
<td>33</td>
<td>0.2</td>
<td>34</td>
</tr>
<tr>
<td>T = 10</td>
<td>23</td>
<td>0.7</td>
<td>24</td>
</tr>
<tr>
<td>T = 20</td>
<td>19</td>
<td>0.6</td>
<td>21</td>
</tr>
<tr>
<td>T = 30</td>
<td>18</td>
<td>0.6</td>
<td>20</td>
</tr>
<tr>
<td>T = 45 (start chemotherapy)</td>
<td>18</td>
<td>0.7</td>
<td>20</td>
</tr>
<tr>
<td>T = 75</td>
<td>17</td>
<td>0.7</td>
<td>19</td>
</tr>
<tr>
<td>T = 105 (stop chemotherapy)</td>
<td>17</td>
<td>0.7</td>
<td>19</td>
</tr>
<tr>
<td>T = 135</td>
<td>17</td>
<td>0.7</td>
<td>19</td>
</tr>
<tr>
<td>T = 165</td>
<td>17</td>
<td>0.6</td>
<td>19</td>
</tr>
<tr>
<td>T = 195 (stop scalp cooling)</td>
<td>17</td>
<td>0.6</td>
<td>19</td>
</tr>
</tbody>
</table>

**Table 3**

Mean scalp skin temperatures in degrees Celsius after 45 min pre-infusion cooling according to the number of chemotherapy cycles.

<table>
<thead>
<tr>
<th>Cycle</th>
<th>No head covering</th>
<th>Head covering</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N = 52)</td>
<td>17</td>
<td>1.1</td>
<td>19</td>
</tr>
<tr>
<td>(N = 29)</td>
<td>18</td>
<td>1.9</td>
<td>21</td>
</tr>
<tr>
<td>(N = 22)</td>
<td>17</td>
<td>1.1</td>
<td>20</td>
</tr>
<tr>
<td>(N = 9)</td>
<td>18</td>
<td>1.8</td>
<td>21</td>
</tr>
<tr>
<td>(N = 7)</td>
<td>18</td>
<td>3.7</td>
<td>19</td>
</tr>
<tr>
<td>(N = 7)</td>
<td>20</td>
<td>1.0</td>
<td>20</td>
</tr>
<tr>
<td>Mean cycle 1–6</td>
<td>18</td>
<td>0.7</td>
<td>20</td>
</tr>
</tbody>
</table>

**Table 4**

Tolerance and side effects of scalp cooling.

<table>
<thead>
<tr>
<th>No</th>
<th>(%)</th>
<th>Tolerance (VAS 0–10) ± SD</th>
<th>N (±10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>Intolerance</td>
<td>1 (2)</td>
</tr>
<tr>
<td>2</td>
<td>37</td>
<td>Chemotherapy finished or interrupted</td>
<td>23 (37)</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>Other</td>
<td>4 (6)</td>
</tr>
</tbody>
</table>

\(a\) 0 represents ‘not tolerable’ and 10 means ‘very well tolerable’.

---

![Fig. 2](image-url) Mean scalp skin temperatures in degrees Celsius during scalp cooling in patients with and without head covering.
temperatures than patients with hair loss. These results are in line with the study of Gregory et al. [9] who investigated scalp cooling by frozen cryogel packs in 24 patients treated with doxorubicin and vincristine. They observed a consistent temperature in each patient after repeated cooling with maximal cooling after 20–30 min. Intradermal scalp skin temperature varied from 19 to 29 °C with significantly lower temperatures in patients with good hair retention (21 versus 24 °C, P < 0.001). Other studies on scalp skin temperature were performed in healthy man, not treated with chemotherapy (Table 5). We could not detect a precise threshold temperature below which hair preservation was likely. However, the best results seem to be obtained when the scalp temperature decreases below 18 °C. In reports on scalp cooling, many authors refer to Gregory et al. [9] with 22 °C subcutaneously (19 °C epicutaneously) as a threshold temperature which patients have to reach for effective cooling. This cut-off point is based on one study with a limited number of patients treated with chemotherapy regimens with lower dosages than used nowadays and outdated scalp cooling techniques. Our results confirm this cut-off point with modern scalp cooling techniques and adequately dosed chemotherapy regimens.

There is currently no satisfactory explanation for the wide scalp temperature variation between patients. Some persons consistently respond to scalp cooling with only a minor reduction in subcutaneous temperature. This might be due to a greater insulative power of the hairs or dermis [7]. It might also be due to enhanced dissipation of heat structures below the subcutaneous tissue, or due to thermal reflex differences with regard to skin perfusion [7]. Janssen et al. [19] explain the variation by anatomical differences such as head shape and thickness of the insulating fat layer. However Gregory et al. [9] report that the large variation in scalp temperature between patients in their study could not be explained by differences in hair thickness or density of scalp tissue.

Although large variations were found between patients in our study, the reached degree of cooling in individual patients was very consistent on repeated cycles of chemotherapy. Differences between patients were therefore not due to changes in the procedure.

Initial hair mass as measured by the Hair Check was not predictive for the severity of hair loss during scalp cooling. Therefore, the efficacy of scalp cooling in preventing CIA is independent of having either thin or thick hair.

Accurate measurement of the scalp skin temperature during scalp cooling is difficult. Needle thermometers can be inserted into the scalp skin to investigate the intradermal temperature [7,9–11,20]. These measurements record the exact temperature without bias from the temperature of the cooling cap, but results of different studies are difficult to compare and these intradermal measurements are a burden for patients. Surface temperatures are patient friendly and can be recorded by using thermocouples attached to the skin [7,10–13,20,21]. These measurements are easier to compare, but a major disadvantage is the probable influence of the cooling cap. However, Bulow et al. [7] demonstrated a close relationship between the epicutaneous and the subcutaneous temperatures during cooling, indicating that the influence of the cooling cap can be neglected.

The position of the temperature probes on the scalp is poorly described in most studies. Researchers do not indicate in which region of the scalp the probes were placed. When described, the frontal and parietal region are mostly used to measure scalp skin temperature [7,10,13,21]. The top of the head is found to be less responsive to cooling [10,13,17]. Massey [13] observed that the temperature at the top of the head was 1 °C higher than at other places of the scalp. This region is most extensively affected by alopecia as we also observed at images that were taken at different time points in the study (Fig. 3). Despite this, there seemed no difference in the need for a head covering between patients with

![Fig. 3](image-url)

**Fig. 3.** The top of the head is most extensively affected by alopecia.
global or patchy hair loss. The probes in our study were placed on the left and right side of the head, which was found to be a temperature-stable region according to Ekwall et al. [10]. A third measurement would have been an interesting addition to find out whether the temperature variability between the temporal area and the crown might have been a predicting factor for the requirement of a head covering. Unfortunately, for practical reasons, only the temporal scalp skin temperatures were measured. This is simultaneously a limitation of our study as relation to the crown temperature remains unknown as well as its prediction for requirement of head covering.

Scalp cooling was very well tolerated (VAS = 8). Nevertheless 15 patients (24%) reported a (mostly mild) headache somewhere during at least one of their cycles. However, only one patient stopped scalp cooling because of intolerance, which is comparable with the literature [8,13,22]. The use of paracetamol as premedication is no standard care in the chemotherapy regimens used in this study. Only fourteen percent of all patients in the study used paracetamol somewhere during their cycles to prevent headaches. This rejects the argument of doctors and nurses who do not to offer scalp cooling because it would be too hard to tolerate [23].

Conclusion

When using scalp cooling to prevent anthracycline-induced alopecia, patients with satisfactory hair preservation appeared to have a significantly lower mean scalp skin temperature (18 °C; SEM: 0.7) during cooling than patients with alopecia (20 °C; SEM: 0.5) (P = 0.01). To obtain optimal results of scalp cooling to prevent chemotherapy induced alopecia, a scalp skin temperature of at least 18 °C should be reached. Apart from the type or dose of chemotherapy, the obtained scalp skin temperature during scalp cooling is a very important factor to prevent hair loss. Improvements in scalp cooling machines should focus on possibilities to measure scalp skin temperature and the possibility to adapt cooling temperature in individual patients.

Compliance with ethical standards

The study was approved by an independent ethics committee and in accordance review board. All procedures were conducted in accordance with the 1964 Helsinki Declaration and its subsequent amendments. Written informed consent was obtained from all individual participants included in the study.

Conflict of interest statement

The authors declare that they have no conflict of interest.

References


