The Breast 30 (2016) 105–110

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Original article

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 31 °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

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

* Corresponding author. Fax: +31 (0)72 5482079.
E-mail addresses: M.M.C.Komen@nwz.nl (M.M.C. Komen), c.smorenburg@nki.nl (C.H. Smorenburg), jwrnortier@casema.nl (J.W.R. Nortier), t.vander.ploeg@nwz.nl (T. van der Ploeg), C.vandenHurk@iknl.nl (C.J.G. van den Hurk), Koos.vanderHoeven@radboudumc.nl (J.J.M. van der Hoeven).

http://dx.doi.org/10.1016/j.breast.2016.09.007
0960-9776/

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° 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/m^2 at 3-weekly intervals or with AC combination chemotherapy with doxorubicin at a dose of 60 mg/m^2. Subsequent chemotherapy cycles consisting of docetaxel monotherapy (100 mg/m^2) 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, cryoglobulinaemia, cryofibrinogenaemia 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).