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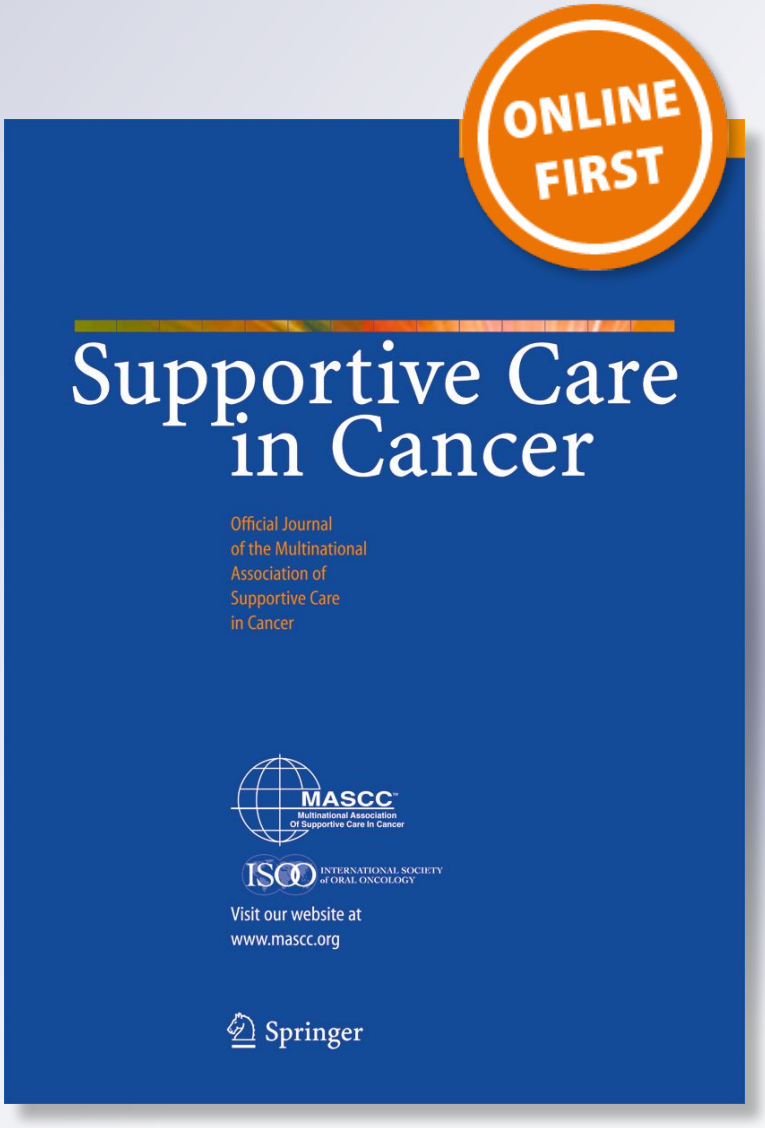

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ORIGINAL ARTICLE

Prolonging the duration of post-infusion scalp cooling in the prevention of anthracycline-induced alopecia: a randomised trial in patients with breast cancer treated with adjuvant chemotherapy

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Abstract

Purpose Scalp cooling as a method to reduce the incidence of chemotherapy-induced alopecia (CIA) is increasingly used in daily practice worldwide. However, in patients treated with 5-fluorouracil, epirubicin and cyclophosphamide (FEC), scalp cooling fails in 48–67% of patients. This study investigated the efficacy of extended duration of post-infusion scalp cooling in breast cancer patients treated with this regimen.

Methods In this prospective multi-centre randomised study, 102 patients with early breast cancer treated with adjuvant FEC chemotherapy were randomly assigned in a 1:1 ratio to a post-infusion cooling time of 90 or 150 min. The primary endpoint was the need to wear a wig or other head covering to mask visible hair loss.

Results Sixteen out of 48 patients (33%) treated with 90 min of post-infusion cooling did not need any head covering, compared with 21 out of 46 patients (45%) treated with 150 min of post-infusion cooling ($p = 0.2$). WHO grades 2–3 (moderate-complete) alopecia were reported more often in patients treated with 90-min post-infusion cooling time ($n = 25/51$ (49%) versus $n = 17/51$ (33%); $p = 0{,}02$). Scalp cooling was well-tolerated (mean Visual Analogue Score 7.4) and only three patients (3%) stopped due to intolerance during treatment.

Conclusions Extending the duration of 90-min post-infusion scalp cooling to 150 min in patients treated with adjuvant FEC chemotherapy was well-tolerated but did not significantly diminish the need for head covering. However, grades 2–3 alopecia was seen less often with prolonged post-infusion scalp cooling.

Keywords Chemotherapy · FEC · Scalp cooling · Alopecia · Hair loss · Breast cancer

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Introduction

As there is a growing awareness for optimal supportive care in patients with cancer, research increasingly focusses on minimising side effects of chemotherapy to improve quality of life [1]. The social and psychological consequences of chemotherapy-induced alopecia (CIA) are obvious to everyone and may affect body image and acceptance of treatment [1–4]. Scalp cooling as a method to reduce the incidence of CIA is increasingly being used in daily practice worldwide [5–7]. The mechanism of scalp cooling during treatment with chemotherapy is based on the theory that reducing the scalp skin temperature during the administration of chemotherapy affects the exposure to and metabolism of cytotoxic agents in the hair follicles [8, 9]. The hair-preserving effects of scalp cooling are highly variable, mainly depending on type and dose of chemotherapy and probably also on the temperature and duration of cooling [9–12]. Scalp cooling has only limited beneficial effect in patients who are treated with anthracyclines [13].

Epirubicin, a frequently used anthracycline, is a semisynthetic derivate of doxorubicin and has a wide range of antitumor activity [14, 15]. Being effective in the treatment of breast cancer, it is frequently used as adjuvant therapy in patients with early breast cancer or palliative chemotherapy for metastatic disease [15]. The drug may be administered alone or in combination with other agents. In the adjuvant setting for breast cancer, a commonly used anthracycline-containing combination chemotherapy regimen is 5-fluorouracil together with epirubicin and cyclophosphamide (FEC) [14]. Standard dose of the FEC regimen consists of fluorouracil 500–600 mg/m^2, epirubicin 90–100 mg/m^2 and cyclophosphamide 500–600 mg/m^2 administered intravenously once every 3 weeks. A very common side effect of this regimen is complete alopecia [14]. Theoretically, the duration of scalp cooling after the infusion of chemotherapy should be related to pharmacokinetics of exposure to the cytostatic agent and its active metabolites [9, 11]. The pharmacokinetics of epirubicin fit a tri-exponential curve with half-lives for the initial (α), intermediate (β) and terminal (γ) elimination phases of approximately 3 min, 1 h and 30 h, respectively [14], but show considerable inter-individual variation [15]. Consequently, recommendations for post-infusion scalp-cooling times are often based upon past experience or are arbitrary [13, 16]. Indeed, in daily practice post-infusion cooling times range from 15 min to 4 h [10]. In The Netherlands, a duration of 90 min of post-infusion cooling time has been arbitrarily chosen as the standard post-infusion cooling time for any chemotherapy regimen. FEC chemotherapy is frequently used as adjuvant treatment in patients with breast cancer and scalp cooling is increasingly being used in this setting to prevent CIA. However, scalp cooling fails in 48–67% of patients treated with this chemotherapy regimen [13]. To investigate whether the efficacy of scalp cooling could be improved by a longer post-infusion time we compared a post-infusion cooling time of 150 min versus 90 min in patients treated with adjuvant FEC chemotherapy.

Methods

Patients

The study enrolled female patients with primary breast cancer, aged 18 or older. They were planned for a minimum of three cycles FEC chemotherapy with an epirubicin dose of 90–100 mg/m^2 at three weekly intervals and were willing to use scalp cooling to prevent CIA. Patients with alopecia before the start of the study were excluded from the study. Also, excluded were patients with (concomitant) haematological malignancies or contraindications for scalp cooling such as cold sensitivity, cold agglutinin disease, cryoglobulinaemia, cryofibrinogenaemia or cold posttraumatic dystrophy.

Study design

We conducted a prospective multi-centre randomised study in seven hospitals in The Netherlands. The primary endpoint of this study was the need to wear a wig or other head covering to mask visible hair loss. The severity of hair loss was evaluated on the 4-point scale for alopecia (0 = no change, 1 = minimal hair loss, 2 = moderate, patchy alopecia, 3 = complete alopecia) of the World Health Organisation [17]. Tolerance of scalp cooling was measured on a 1–10 Visual Analogue Scale (VAS), with 10 being the most tolerable. Other side-effects such as headaches were also recorded. Patients were considered eligible for final analyses if they were treated with at least two cycles of FEC chemotherapy or if they discontinued scalp cooling after one cycle due to severe hair loss. Patients were randomly assigned to a post-infusion cooling time of 90 min or 150 min with the allocation ratio of 1:1 (Fig. 1). The random sequence was carried out following a predefined randomisation schedule by an external independent centre (Netherlands Comprehensive Cancer Network (IKNL)). Each institutional review board approved the study before participants were enrolled. All procedures were conducted in accordance with the 1964 Helsinki Declaration and its later amendments. Patients were informed about the study by specialised oncology nurses. All patients gave written informed consent prior to enrolment and randomisation.

Intervention

The Paxman one-person cooling machine (PSC-1), with a standard temperature of − 10 °C was used in this study by all participating hospitals. Oncology nurses applied the cool cap according to the instructions for use in the nursing protocol. The pre-cooling time was 30 min before the start of the

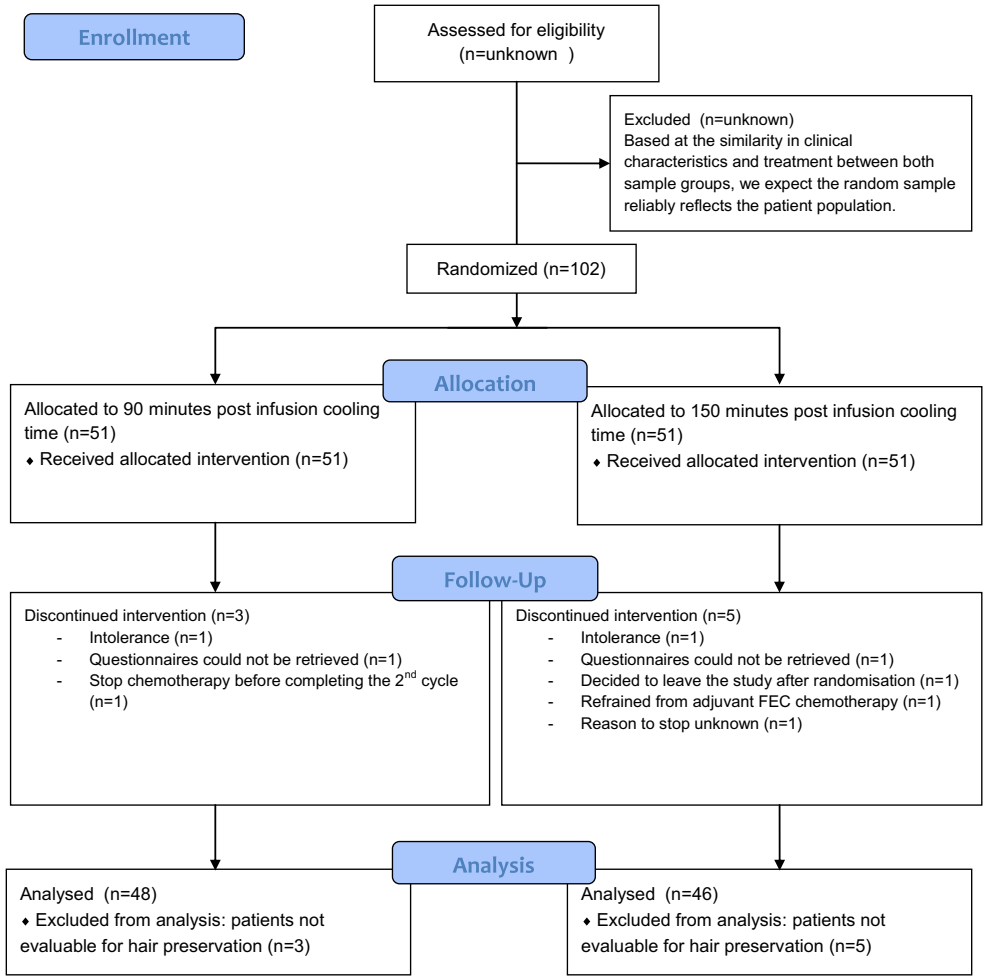

Fig. 1 Consort 2010 flow diagram

chemotherapy infusion and the cool cap remained on the scalp during the infusion period of 60 min. Scalp cooling was applied during all planned cycles of chemotherapy, unless the patient decided to stop the cooling procedure because of hair loss, side-effects or for patients' preference.

Sample size and statistical analysis

The sample size was calculated for the different cooling times. A power and sample size program was used to estimate the sample size (PS: Power and sample size calculation) [18]. The primary endpoint was the need to wear a wig or other head covering to mask visible hair loss. Based on data from our registration study, the risk of hair loss for patients treated with the standard scalp cooling was approximately 50%. We assumed that an improvement of at least 30% in the outcome of scalp cooling would be clinically relevant to justify the burden of a prolonged post-infusion scalp cooling time of 150 min. With a power set at 80%; a 30% difference could be detected in 44 patients in each randomisation arm. Based on the expected drop-out after inclusion, 51 patients per arm were included. All outcomes were analysed with two-tailed tests at $\alpha = 0.05$, and differences were considered statistically significant when $p < 0.05$. Analyses were performed using SPSS software (version 20.0) for Windows XP. Patient and treatment characteristics were analysed using a Chi-square test. Response to scalp cooling and tolerance were analysed using the Mann-Whitney test. Age and follow-up were analysed using a t-test. The analyses were carried out on all randomised patients on an intention-to-treat (ITT) basis, while a secondary analysis was performed on the subgroup of patients receiving at least 2 cycles of chemotherapy and scalp cooling.

Results

Patient and treatment characteristics

Between March 2007 and July 2015, a total of 102 female patients were randomised to a post-infusion cooling time of 90 or 150 min. All patients were treated in accordance with the

Table 1 Patient and treatment characteristics

	90 min post-infusion cooling time ($n = 51$)	150 min post-infusion cooling time (n = 51)	p value
Mean age, years (range)	51 (30–72)	52 (40–69)	
Chemotherapy (type)			1.0
5× FEC	18 (35%)	18 (35%)	
6× FEC	17 (33%)	18 (35%)	
3× FEC followed by 3× TXT	16 (32%)	15 (30%)	
Chemotherapy (dose)			0.7
F(500[a])E(90[a])C(500[a])	21 (41%)	19 (37%)	
F(500[a])E(100[a])C(500[a])	30 (59%)	32 (63%)	
Median number of cycles with scalp cooling ± SD	3 ± 0.2	5 ± 0.3	

[a] mg/m^2

assigned randomisation of post-infusion duration of scalp cooling. Patient and treatment characteristics are listed in Table 1. The mean age was 52 years. Thirty-six out of 102 patients (35%) were treated with five cycles FEC with an epirubicin dose of 90 mg/m^2, 35 patients with 6 cycles FEC with an epirubicin dose of 100 mg/m^2, and 31 patients with three cycles FEC (epirubicin dose 100 mg/m^2) followed by three cycles docetaxel. There was no significant difference between patients in the 90- and 150-min groups with respect to treatment characteristics. All patients treated conform to the study protocol with scalp cooling during FEC chemotherapy, for a median of four cycles. At the time of the data cut-off (December 7, 2015), the median follow-up of patients was 73 months.

Efficacy analysis

In this study, eight patients (7.8%) were not evaluable for hair loss. Two patients stopped scalp cooling due to intolerance before the second cycle was completed, one patient refrained from adjuvant FEC chemotherapy, one patient stopped chemotherapy before the second cycle was completed, one patient decided to leave the study after randomisation, two questionnaires could not be retrieved and in one patient, the reason to stop was unknown.

Finally, a total of 94 out of 102 included patients was evaluable for hair preservation (Table 2). Thirty-seven out of 94 evaluable patients (40%) did not need to wear a wig or other head covering to mask hair loss during their therapy. There was no significant difference in the proportion of patients who wore a wig or head cover between the 90-min group and the 150-min group ($n = 16/48$ (33%) versus $n = 21/46$ (45%); $p = 0.2$). The WHO score for alopecia grades 2–3 (moderate-complete) was reported significantly more often in patients treated with 90-min post-infusion cooling time ($n = 25/51$ (49%) versus $n = 17/51$ (33%); $p = 0{,}02$). The planned number and type of adjuvant chemotherapy (5× FEC, 6× FEC or 3× FEC followed by 3× docetaxel) did not correlate with the need to wear head covering ($p = 0.08$). The need to wear head covering was 47% in patients treated with epirubicin at a dose of 90 mg/m^2 compared to 69% in patients treated with 100 mg/m^2 ($p = 0.04$) (Table 3).

Table 2 Response to scalp cooling

	90 min post-infusion cooling time (n = 51)	150 min post-infusion cooling time (n = 51)	p value
Evaluable for scalp cooling efficacy	48	46	
Head covering			0.2
Patients with head covering	32 (67%)	25 (55%)	
Patients without head covering	16 (33%)	21 (45%)	
Not evaluable	3 (6%)	5 (10%)	
WHO[a] for alopecia			0.02
0–1	10 (20%)	23 (45%)	
2–3	25 (49%)	17 (33%)	
Missing	16 (31%)	11 (22%)	

[a] WHO, offset publication no.48 [17]

Table 3 Efficacy of scalp cooling depending on type and dosage of chemotherapy in 94 evaluable patients

	No head covering ($n = 48$)	Head covering ($n = 46$)	p value
Chemotherapy (type)			0.08
5× FEC	18 (55%)	15 (45%)	
6× FEC	10 (32%)	21 (68%)	
3× FEC followed by 3× TXT	9 (30%)	21 (70%)	
Chemotherapy (dose)			0.04
90 mg/m^2	19 (53%)	17 (47%)	
100 mg/m^2	18 (31%)	40 (69%)	

Tolerance and safety analysis

Scalp cooling was well-tolerated irrespective of the post-infusion duration (Table 4). Tolerance of scalp cooling, recorded by a VAS score was performed after 322 cooling procedures, and resulted in a mean score of 7.4 (SD: 2.1) There were three patients (3%) who stopped scalp cooling because of intolerance. Side effects such as headaches were recorded during 327 cooling procedures: in 238 sessions (73%), no headaches were reported; while headache was reported as mild, moderate or severe in 66 (20%), 20 (6%) and 3 (1%) sessions, respectively. There were no scalp metastases reported during the follow-up period.

Discussion

In this randomised study performed in patients with early breast cancer treated with adjuvant chemotherapy with the FEC regimen, prolonging of the duration of 90 min post-infusion scalp cooling to 150 min was well-tolerated but did not significantly diminish the need for head covering. However, grades 2–3 alopecia were observed less often with prolonged post-infusion scalp cooling.

Thirty-seven out of 94 evaluable (40%) patients were successfully treated with scalp cooling to prevent CIA, corresponding with the results (33–52%) of FEC high dose chemotherapy in a large registry study on scalp cooling [13].

Our study has some limitations and may have been underpowered. At the start of the study, the standard chemotherapy regimen in The Netherlands for patients with primary breast cancer was five cycles FEC at an epirubicin dose of 90 mg/m^2. Based on international guidelines, treatment with six cycles FEC at a dose of 100 mg/m^2 was also given in some centers. However, there was no data available on the positive effect of scalp cooling at this higher dose. Therefore, the effect of scalp cooling in the FEC regimen at a dose of 90 mg/m^2, as was available from our registration data (50% efficacy), was used for power calculation. At present, after extension of our registry, the estimation of scalp cooling efficacy in the FEC regimen with epirubicin 90 mg/m^2 proved to be correct (52% efficacy). However, we found that the efficacy of scalp cooling in the FEC regimen with epirubicin 100 mg/m^2 is 33% [13]. Therefore, a significant difference in efficacy might have been missed.

In our study, grades 2–3 alopecia were seen less often with prolonged post-infusion scalp cooling. Therefore, we cannot exclude a clinical meaningful difference between the two post-infusion cooling times. This should be explored further in studies with a larger sample size and quantitative methods to measure the degree of hair loss. However, even if the effect of 150-min post-infusion cooling would indeed be superior in a larger study, one should consider the long stay in the hospital which is less feasible for both patients and nurses and goes with increased costs for hospitals due to extended duration of nursing time and stay at the chemotherapy unit.

Table 4 Tolerance, side-effects and follow-up

	90 min post-infusion cooling time (n = 51)	150 min post-infusion cooling time (n = 51)	p value
Tolerance (VAS 0-10[a]) ± SD	7.5 ± 2.0	7.3 ± 2.2	0.8
Reasons to stop scalp cooling other than hair loss			b
Intolerance	1 (2%)	2 (4%)	
Chemotherapy finished or interrupted	25 (49%)	27 (53%)	
Other	1 (2%)	5 (10%)	
Median follow-up, months (range)	74 (15–106)	72 (8–108)	1.0

[a] 0 represents 'not tolerable' and 10 means 'very well tolerable'

[b] Chi-square results are invalid because of cell counts less than five

The follow-up in this study is very long (73 months, range 8–108 months), and can be explained by the long inclusion period of the study. Contrary to our expectations, it was difficult to motivate patients to be randomised between 90- and 150-min post-infusion cooling times. This extended the period of inclusion in which the dose of FEC initially changed from 90 mg/m^2 to 100 mg/m^2 and later changed to a sequential schedule of three courses FEC with 100 mg/m^2 epirubicin, followed by three courses docetaxel mono-therapy of 100 mg/m^2.

In recent years, the hair check method has become available for objective hair loss measurement [19]. An objective and more sensitive method of measuring hair loss may especially be of value in the research on refining scalp cooling techniques to prevent CIA. However, patient reported outcome as a parameter for patient satisfaction remains the most important clinical criterion for the efficacy of scalp cooling. In order to compare scalp cooling outcomes, preferably a combination of a subjective clinical scale and an objective method like the hair check should be used, at least in clinical studies.

Several reports on the anthracycline pharmacokinetics point out the large inter-individual variations and the need for individualization of the doses based on measured plasma concentrations [20, 21]. Eksborg et al. measured that an increase in maximum plasma concentration of epirubicin was associated with an increasing degree of alopecia [22]. Therefore, it might be interesting to investigate whether adapting the post-infusion cooling time to the maximum plasma concentration could improve scalp-cooling outcomes.

The procedure of scalp cooling was very well-tolerated (VAS = 7.4) and independent of duration of post-scalp cooling. Nevertheless, 48 patients reported any grade headache (mostly mild) during at least one of their cycles. Only three patients stopped scalp cooling because of intolerance, both in line with the literature [6, 9, 12, 16, 23, 24].

In conclusion, our study did not significantly contribute to an overall favourable clinical effect of scalp cooling in reducing the use of head covering. However, it demonstrated that prolonging the post-infusion cooling time of the FEC (90–100 mg) regimen did show some reduction of grade 2/3 alopecia after 150 min.

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Compliance with ethical standards

Procedures performed in this study were in accordance with the 1964 Helsinki Declaration and its later amendments and in accordance with the ethical standards of the institutional review board and independent ethics committee. All participants gave written informed consent prior to enrolment and randomisation.

Conflict of interest The authors declare that they have no conflict of interest.

The authors have full control of all primary data and agree to allow the journal to review their data if requested.

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