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ORIGINAL ARTICLE

Results of 20- versus 45-min post-infusion scalp cooling time in the prevention of docetaxel-induced alopecia

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Abstract
Purpose For patients, chemotherapy-induced alopecia (CIA) is one of the most distressing side effects of treatment. Scalp cooling can prevent or minimise CIA; the results may depend on the duration of cooling. Since a previous study on post-infusion cooling time in patients treated with docetaxel chemotherapy found no difference between 90 and 45 min, we investigated whether hair-preserving results could be maintained with a shorter post-infusion cooling time.
Methods In this prospective, multi-centre randomised study, 134 patients who started treatment with docetaxel 75–100 mg/m^2 in a 3-weekly schedule were randomly assigned in a 1:1 ratio to a post-infusion cooling time of 45 or 20 min. The primary end point was the need for a wig or other head covering as assessed by the patient. A visual analogue scale (VAS) with a range from 0 (not tolerable) to 10 (very tolerable) was used to measure tolerance.
Results Scalp cooling results were similar for 45- and 20-min post-infusion cooling times. Thirty-three out of 45 patients (73 %) treated with 20 min of post-infusion cooling did not need a form of head covering, compared with 41 out of 52 patients (79 %) treated with 45 min of post-infusion cooling ($p = 0.5$). The procedure was well tolerated (mean visual analogue score 8.3). Six patients stopped due to intolerance during the first treatment cycle.
Conclusions A 20-min post-infusion cooling time is effective and tolerable for patients treated with scalp cooling to prevent docetaxel-induced alopecia.
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Introduction

For patients, chemotherapy-induced alopecia (CIA) is one of the most distressing side effects of treatment. It has psychosocial implications and may affect body image and acceptance of treatment [1–4]. In the past two decades, a considerable amount of intensive research has been conducted into other chemotherapy-related side effects, such as nausea and fatigue. The treatment of these symptoms has since improved. CIA remains an issue that is difficult to resolve. For some patients, CIA is a reason to refuse certain types of chemotherapy [5, 6]. Despite the importance of hair loss for patients, alopecia is infrequently mentioned in phase II and III oncology trials. Although CIA is not life threatening and rarely leads to rejection of chemotherapy, it should be incorporated as an important patient-reported outcome measure in pharmaceutical trials. When there are no survival benefits between cytotoxic treatments, quality-of-life issues such as CIA might be decisive [7].

Scalp cooling is used to prevent CIA (Fig. 1) [8]. It is assumed that it reduces skin temperature, thereby affecting the exposure and metabolism of cytotoxic agents in the hair follicles [9, 10]. The hair-preserving effects of scalp cooling are variable, mainly depending on the type and dose of chemotherapy and probably on the degree and duration of cooling [10–12]. In theory, the scalp should remain cooled until the level of active drug or its metabolites is reduced to sufficiently low levels in the plasma.

Docetaxel is a semi-synthetic taxoid and is effective against various cancers [13, 14]. It is usually administered as a 1-h intravenous infusion repeated every 21 days, at a recommended dose of 75 or 100 mg/m^2 depending on tumour type and use as a single or combined agent. Docetaxel-induced alopecia is common at doses higher than 55 mg/m^2 and has been observed in over 80 % of patients at doses higher than 70 mg/m^2 [13–17]. The pharmacokinetics of docetaxel fit a triexponential curve: the α, β and γ half-lives with a 115 mg/m^2 1-h infusion are 4, 36 and 22 h, respectively [14]. As data regarding the concentration and duration of exposure of docetaxel that causes alopecia are lacking, the optimum scalp cooling time remains unclear. In addition, there is considerable intra-individual variation in half-life times among patients who are treated with docetaxel [14]. Consequently, recommendations for scalp cooling times are often based upon past experience or are arbitrary [18, 19]. In daily practice, post-infusion cooling times range from 15 min to 4 h [11]. Scalp cooling has a hair-preserving result in 61–94 % of docetaxel-treated patients with a post-infusion cooling time of 15–90 min and depends on dose and treatment schedule [12, 19–22].

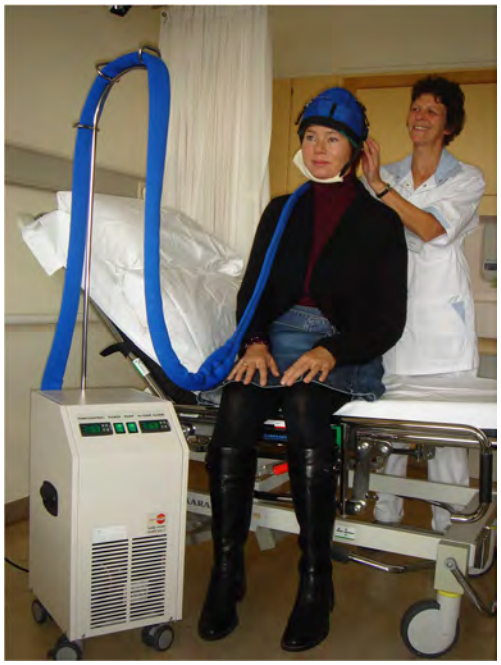

Fig. 1 Paxman (PSC-1) cooling device equipped with a thermostat

The duration of post-infusion cooling implies a prolonged stay on the chemotherapy ward; this is potentially a disadvantage both for patients and for the logistics of the clinic. As a previous study on post-infusion cooling time in patients treated with docetaxel chemotherapy found no difference between 90 and 45 min, we investigated whether hair-preserving results could be maintained with an even shorter post-infusion time of 20 min [22].

Patients and methods

Patients were enrolled in this prospective multi-centre randomised study between October 2009 and May 2013. 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. Specialised oncology nurses informed patients about the study. Written informed consent was obtained from all individual participants included in the study. Inclusion criteria were that patients were undergoing docetaxel-containing schedules at 3-weekly intervals and were aged 18 or over. Exclusion criteria were treatment with docetaxel in sequential schemes (docetaxel monotherapy after 5-fluouracil, epirubicin, cyclophosphamide (FEC) or after adriamycin, cyclophosphamide (AC)), treatment with docetaxel combined with adriamycin and cyclophosphamide (TAC), alopecia before the start of the study, haematological malignancies and rare disorders like cold sensitivity, cold agglutinin disease, cryoglobulinaemia, cryofibrinogenaemia and cold posttraumatic dystrophy. Eligible patients who chose

scalp cooling were randomly assigned to a post-infusion cooling time of 45 or 20 min in a 1:1 ratio. The random sequence was kept by an external centre (Comprehensive Cancer Organisation Netherlands, IKNL, location Eindhoven).

All 16 participating hospitals used the Paxman one-person cooling machine (PSC-1). The cap was applied according to the instructions for use in the nursing protocol. The temperature of the coolant in the refrigeration tank was −10 °C. This temperature is a standard set-up installed by the manufacturer. The pre-cooling time was 30 min before the start of the chemotherapy infusion. The cool cap remained on the scalp during the infusion period, 60 min being the standard. Scalp cooling was applied during all planned cycles of chemotherapy, unless the patient decided to stop the cooling procedure based on hair loss, side effects, or for other reasons.

The success of scalp cooling was defined in terms of the patient's self-determined need to wear a wig or other head covering (e.g. hat or scarf) to mask visible hair loss after docetaxel treatment. Patients additionally evaluated hair loss on the 4-point scale for alopecia (0 = no change, 1 = minimal hair loss, 2 = moderate, 3 = patchy alopecia, 4 = complete alopecia) of the World Health Organisation (WHO; offset publication no. 48) [23]. Patients were considered eligible for evaluation of hair preservation if they were treated with at least 2 cycles of docetaxel chemotherapy or if they discontinued scalp cooling after 1 cycle due to severe hair loss. Tolerance of scalp cooling was measured by a (self-adapted) 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.

Statistical analysis

The primary end point was the need to wear a wig or other head covering as assessed by the patient. Nominal variables like hair loss, gender, and chemotherapy were analysed using a chi-square test. Ordinal variables, like the 10-point VAS, WHO and pre- and post-infusion cooling times 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. The power of the test was estimated as 80 % with a two-sided α value of 0.05, which indicated a sample size of 40 evaluable subjects in each arm. Based on the number of patients who were not completely evaluable in an earlier multicentre scalp cooling trial [22], we considered a sample size of 60 patients per arm. Finally, 97 out of 134 included patients were evaluable for hair preservation. Data were collected using standard forms, which were compiled into a SPSS database. 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

In this study, a total of 134 patients treated with docetaxel chemotherapy were entered and randomised to a post-infusion cooling time of 45 or 20 min. The study was ended when the pre-determined number of enrolled subjects was obtained. Patient characteristics are listed in Table 1. The median age of patients was 64 years. There were no significant differences between the 45- and 20-min group with respect to clinical characteristics and treatment. Most patients were treated for prostate cancer (43 %) and received docetaxel monotherapy (84 %). All patients were treated in accordance with the assigned randomisation. The median pre-infusion cooling time was 33 min (IQR 15).

At the time of data analysis (8 April 2014), the median follow-up for patients in the 20-min group was 6.5 months and 7.5 months for the 45-min group (Table 2). Thirty-seven patients were not evaluable for hair preservation. Five patients stopped due to intolerance during the first chemotherapy cycle, 21 patients stopped chemotherapy before completing the second cycle, one patient died before hair loss could be reported, three patients decided to leave the study after randomisation, one patient was not treated with docetaxel, one patient withdrew informed consent and five questionnaires could not be retrieved.

In this study, 97 patients were evaluable for hair preservation (Table 3). There was no significant difference in the need to wear head covering in the 20-min group compared to the 45-min group (20 min, $n = 33/45$ (73 %) no head covering; 45 min, $n = 41/52$ (79 %) no head covering; $p = 0.5$). A significant difference in the need to wear head covering was seen when the dosages of docetaxel (75 mg/m^2, $n = 5/65$ (8 %); 100 mg/m^2, $n = 14/25$ (57 %); $p < 0.0001$) and gender (males, $n = 59/62$ (95 %); females, $n = 15/35$ (43 %); $p < 0.0001$) were compared (Table 4).

During the follow-up period, information on hair status was not available while scalp metastases were not reported. Scalp cooling was well tolerated. A VAS score for tolerance of scalp cooling was performed 471 times, resulting in a mean score of 8.3 (Table 2). Information concerning headache was reported 488 times: in 417 (85 %) sessions, patients reported no headache; in 55 sessions (11 %) minimal; in 14 (3 %) moderate; and in 2 (0.4 %) sessions patients reported severe headaches. No other side effects were reported.

Table 1 Patient characteristics

	20-min post-infusion cooling time ($n = 64$)	45-min post-infusion cooling time ($n = 70$)	*P* value
Mean age, years (range)	64 (43–82)	64 (25–83)	1.0
Gender			0.3
Male	36 (56 %)	46 (66 %)	
Female	28 (44 %)	24 (34 %)	
Cancer			0.6
Breast	17 (27 %)	20 (28 %)	
Lung	13 (20 %)	9 (13 %)	
Prostate	26 (41 %)	32 (46 %)	
Gastrointestinal	1 (1 %)	1 (1 %)	
Others	2 (3 %)	2 (3 %)	
Missing	5 (8 %)	6 (9 %)	
Chemotherapy			0.7
Docetaxel monotherapy	55 (86 %)	58 (83 %)	
Docetaxel combination therapy[a]	6 (9 %)	8 (11 %)	
Missing	3 (5 %)	4 (6 %)	
Setting			0.8
Curative	5 (9 %)	6 (10 %)	
Palliative	53 (91 %)	54 (90 %)	
Median number of cycles with scalp cooling	5	5	[b]

[a] Docetacel combined with doxorubicin, cyclophosphamide, gemcitabin, carboplatin or capecitabine

[b] Chi-square results are invalid because of cell counts less than 5

Discussion

In the present study, 74 out of 97 patients (76 %) treated with scalp cooling did not need a head covering to cover visible hair loss after docetaxel chemotherapy, while no difference was found between 45- and 20-min post-infusion cooling times. As mentioned, a previous study on scalp cooling to prevent docetaxel-induced alopecia found no difference between 90- and 45-min post-infusion cooling times [22]. Of all the patients in that study, 84 % ($n = 129$) did not wear a head covering. Twenty minutes can therefore be advised as a standard post-infusion cooling time for patients treated with 3-weekly docetaxel-containing chemotherapy. This is a major benefit for both patients and hospitals, as patients can be discharged earlier and since the stay in hospital is shorter, more patients can be treated.

Hair preservation was very good, which is in accordance with the results of other scalp cooling studies. Results were better at lower docetaxel dosages as also observed in such other studies [12, 19–22, 24–26]. However, because there was no significant difference between the 45- and 20-min group with respect to dosage, conclusions on shortening post-infusion cooling times remain valid.

Table 2 Tolerance, side effects and follow-up

	20-min post-infusion cooling time ($n = 64$)	45-min post-infusion cooling time ($n = 70$)	*P* value
Tolerance (VAS 0–10[a]) ± SD	8.6 ± 1.4	8.0 ± 9.6	0.1
Headache (any grade)	19 (31 %)	19 (29 %)	1.0
Reasons to stop scalp cooling other than hair loss			[b]
Intolerance	1 (2 %)	5 (7 %)	
Chemotherapy finished or interrupted	46 (72 %)	50 (71 %)	
Others	8 (13 %)	10 (14 %)	
Median follow-up, months (IQR)	6.5 (6.3)	7.5 (6.9)	0.7

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

[b] Chi-square results are invalid because of cell counts less than 5

Table 3 Response to scalp cooling

	20-min post-infusion cooling time ($n=64$)	45-min post-infusion cooling time ($n=70$)	*P* value
Evaluable for scalp cooling	45	52	0.5
Patients with head covering	12/45 (27 %)	11/52 (21 %)	
Patients without head covering	33/45 (73 %)	41/52 (79 %)	
Not evaluable	19 (30 %)	18 (26 %)	
WHO[a] for alopecia			0.8
0	22 (46 %)	24 (45 %)	
1	18 (37 %)	18 (34 %)	
2	7 (15 %)	8 (15 %)	
3	1 (2 %)	3 (6 %)	

[a] WHO; offset publication no. 48 [23]

Scalp cooling was very well tolerated (VAS = 8.3). Nevertheless, 38 patients reported a (mostly mild) headache somewhere during at least one of their cycles. Five patients (5.3 %) stopped scalp cooling because of intolerance, which is comparable with findings in the literature [10, 18, 22]. This refutes the argument of some doctors and nurses who do not offer scalp cooling because it would be too hard to tolerate [27].

Comparing studies concerning hair preservation is complicated by the lack of a standardised methodology for evaluating hair loss [28–30]. To assess hair loss, the authors chose from among several widely accepted scales, such as the WHO classification of chemotherapy-induced alopecia, the Common Terminology Criteria for Adverse Events (CTCAE) and VAS. In the present study, we asked patients whether a wig or head cover was used and we measured the degree of hair loss according to the WHO criteria. Recently, an objective method has become available to measure hair quantity: the cross-section trichometer [31], a very promising technology for research purposes [32]. However, the use of a wig or head cover as a parameter for patient satisfaction should remain the most important clinical criterion for the success of scalp cooling [8]. In future studies concerning scalp cooling and hair preservation, the use of a cross-section trichometer combined with previously used methods is strongly recommended.

In this study, 61 % of patients were males. Contrary to prevailing assumptions, men also describe negative feelings about hair loss. Men's experiences have been largely ignored and healthcare professionals should spend more time assisting men with adjustment to CIA [33]. Men are often treated with docetaxel, a regimen in which the results of scalp cooling proved to be very good (Fig. 2). In this study, 95 % of male patients did not need a head covering, against 43 % of female patients. This is in agreement with previous findings [19].

Table 4 Efficacy of scalp cooling depending on the type and dosage of chemotherapy and gender

	No head covering	Head covering	*P* value
Chemotherapy			[a]
Docetaxel monotherapy	67 (78 %)	19 (22 %)	
Docetaxel combination therapy	7 (70 %)	3 (30 %)	
Docetaxel/gemcitabin	1	0	
Docetaxel/carboplatin	5	2	
Docetaxel/capecitabin	1	0	
Docetaxel/cyclophosphamide	0	1	
Dosage			<0.0001
75 mg/m^2	60 (92 %)	5 (8 %)	
100 mg/m^2	11 (44 %)	14 (56 %)	
Gender			<0.0001
Male	59 (95 %)	3 (5 %)	
Female	15 (43 %)	20 (57 %)	

[a] Chi-square results are invalid because of cell counts less than 5

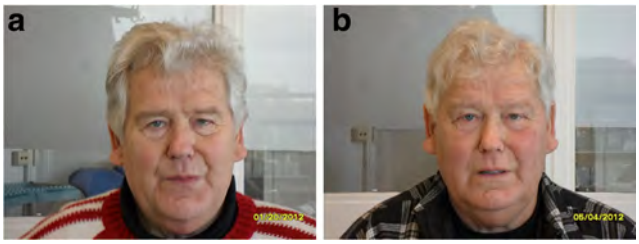

Fig. 2 Results of scalp cooling in a male patient who was treated with docetaxel

However, the result in males may be overestimated, since men are in general less inclined to wear a wig or head covering. As upfront chemo-hormonal therapy for metastatic prostate cancer seems to improve overall survival, even more men will be treated with docetaxel in the future [34]. It would be a major improvement if all men undergoing docetaxel chemotherapy were informed about the highly protective effect of scalp cooling in preventing CIA.

Although the numbers are small, we can formulate a concrete recommendation on post-infusion cooling time for patients treated with docetaxel-containing schedules at 3-weekly intervals. The pre-cooling time should remain at 30 min before the start of the chemotherapy infusion. The post-infusion cooling time can be adapted from 45 to 20 min.

Another interesting aspect for investigation might be scalp cooling without a post-infusion cooling time for cytotoxics with rapid clearance. Scalp cooling decreases the exposure of hair follicles to chemotherapy but might also unnecessarily suppress the hair repair mechanism [22, 35].

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Compliance with ethical standards 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 individual participants included in the study.

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

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