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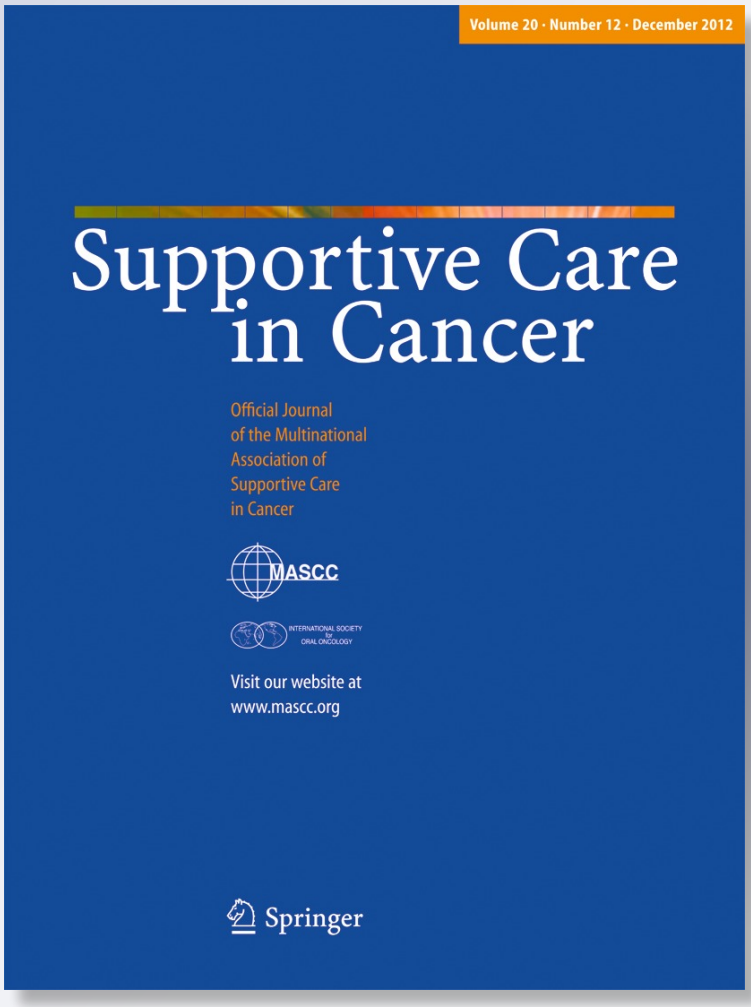

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ORIGINAL ARTICLE

Short post-infusion scalp cooling time in the prevention of docetaxel-induced alopecia

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Abstract
Purpose The patient impact of chemotherapy-induced alopecia (CIA) is high. Scalp cooling is applied to reduce CIA. The potential optimum post-infusion cooling times (PICTs) are currently unknown.
Methods Scalp cooling was applied in 53 patients receiving docetaxel chemotherapy with 90-min PICT (observational part). Also 15 non-scalp-cooled patients were included. If hair preservation was observed in >80 % of the patients, randomisation between 45 and 90-min PICT was planned. Patients reported tolerance of scalp cooling and use of head covering.
Results Observational study: 81 % of scalp-cooled patients did not require head covering versus 27 % of non-scalp-cooled patients. Randomised study: 79 % of 38 patients with 90-min PICT did not need head covering versus 95 % of 38 patients with 45-min PICT (p=0.04). Scalp cooling was very well tolerated (visual analogue scale=79).
Conclusion A 45-min PICT can be recommended in 3-weekly docetaxel regimens with a dose of 75 or 100 mg/m^2, administered in 60 min. The shorter PICT is a major advantage in time investment for patients. Patients (women and men) who receive docetaxel, except combined with doxorubicin and cyclophosphamide (taxotere, adriamycin and cyclophosphamide (TAC)) should be informed about the protective effect and high tolerability of scalp cooling in avoiding CIA.

Keywords Scalp cooling · Chemotherapy-induced alopecia · Docetaxel · Post-infusion cooling time · Hair loss · Supportive care

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Introduction

Chemotherapy-induced alopecia (CIA) is one of the most distressing side effects of chemotherapy. Scalp cooling is applied preceding, during and following chemotherapy to prevent CIA. It is a worthwhile supportive care for cancer patients, as demonstrated by the rapid increase of its use in Europe. The reported success rates of scalp cooling vary widely [1, 2] depending on many factors like the type and dose of cytotoxics and the number of chemotherapy cycles. Theoretically, the influence of post-infusion cooling time (PICT), the time from finishing chemotherapy infusion to finishing scalp cooling, may also be important for the success rates but has never been studied.

Success rates in studies with 3-weekly docetaxel as monotherapy or in combination with other agents are very favourable: 83–100 % of the patients does not require head covering [3–9]. In these studies, PICTs vary from 15 min to 3 h, and in three of the studies, the infusion time was reported to be 60 min. The PICTs are based on clinical impressions and on calculations of half-life times of cytotoxic drugs and their metabolites in the plasma [10]. These calculations seem reasonable because CIA is often dose-dependent, and the concentration of cytotoxic drugs in the hair follicle cells is very likely related to the concentration in the plasma. However, the calculations are questionable because there is a very large patient variability in plasma half-life

times and bioavailability of cytotoxics [11]. Moreover, combination chemotherapy might change the pharmacokinetic profile of docetaxel [10, 12]. In addition, the influence of scalp cooling on pharmacokinetics, pharmacodynamics and toxicity in hair follicle cells is unknown. Optimal PICTs probably also depend on the duration of the cytotoxic infusion rates, but this has never been studied.

Up to now, the only method to develop a PICT advice for a particular chemotherapy schedule is to study the hair preservation results in patients randomised for various PICTs. In this study, we report the tolerance and efficacy of a standard PICT of 90 min in patients receiving docetaxel-containing chemotherapy schedules in daily practice in the Netherlands. In the second part of the study, patients were randomised between a PICT of 45 or 90 min.

Materials and methods

The design was an observational study followed by a randomised study. In the observational part, it was investigated whether hair preservation with a 90-min PICT resulted in less or more than 80 % of the patients not requiring a wig or head cover. If hair preservation was present in more than 80 % of the patients, randomisation between 90 and 45-min PICT was planned. If hair preservation turned out to be present in less than 80 % of the patients, randomisation between 90 and 150-min PICT was planned. Patients included in the observational part did not participate in the randomised study. Randomisation was scheduled in a 1:1 ratio, stratified by hospital. Non-scalp-cooled patients, who rejected scalp cooling, were included as controls during the observational part of the study.

Patients were systematically enrolled between August 2005 and December 2008 in 11 Dutch hospital locations. Inclusion criteria were included intravenously administered 3-weekly docetaxel schedules as a single agent or in combination with other cytotoxics and an age of 18 years or more. Exclusion criteria were included treatment with docetaxel in sequential schemes (subsequent to doxorubicin and cyclophosphamide (AC) or 5-fluorouracil, epirubicin and cyclophosphamide (FEC)), docetaxel combined with doxorubicin and cyclophosphamide (taxotere, adriamycin and cyclophosphamide (TAC)), alopecia before the start of the study, haematological malignancies, clinical signs of scalp metastases, cold sensitivity, cold agglutinin disease, cryoglobulinemia, cryofibrinogenemia and cold posttraumatic dystrophy.

Medical doctors and oncology nurses informed patients about the study. Patients who decided to participate completed a written questionnaire at the day care unit during each chemotherapy session.

The efficacy of scalp cooling was patient-reported and defined by satisfaction with hair preservation, reflected by the use of a wig or head cover during the final scalp cooling session. Patients were considered admissible for evaluation of hair preservation if they had received at least two cycles of chemotherapy or if they discontinued scalp cooling after one cycle due to severe CIA. Hair loss is usually most severe after the first two cycles; thereafter, it stabilises gradually.

Scalp cooling was applied 30 min prior to the chemotherapy infusion until 45 or 90 min after the end of the infusion. In all 11 hospitals, the Paxman scalp cooling system (PSC1 or PSC2) was used.

Patients' acceptability of scalp cooling was assessed by a visual analogue scale (VAS) from 0 for not acceptable to 100 for very well acceptable. In addition, patients were asked on a 4-point Likert scale to what extent they experienced any headache.

The Comprehensive Cancer Centre South (IKZ, Eindhoven) was responsible for randomisation and data collection. Approval for this study was obtained from the Medical Ethics Committees of the participating hospitals, and all enrolled patients provided informed consent. This study was registered as an International Standard Randomised Controlled Trial, number ISRCTN00283877.

Statistical analyses

The proportions of patients with and without head covering were compared between the groups with different PICTs and between scalp-cooled and non-scalp-cooled patients. Differences were tested by the chi-square test or Mann–Whitney *U* test. Randomised patients were analysed according to assigned PICT. Power analysis was based on a 30 % difference in requiring a wig or head cover between the standard treatment of 90 min and the experimental treatment of 45 or 150 min. This difference could be detected by 38 patients in each randomisation arm with 80 % power and alpha=0.05. Statistical analyses were performed using SAS (version 9.1 for Windows, SAS institute Inc., Cary NC).

Results

The characteristics of the patients with and without scalp cooling in the observational part and in the randomised part of the study are depicted in Table 1. The majority of patients had breast cancer (49 %), were treated with docetaxel monotherapy with a dose of 75 mg/m^2 (59 %) and most frequently in the palliative setting (91 %). The infusion time of docetaxel was 60 min in all but one patient, who had 90-min infusion time and was randomised for 90-min PICT. In patients who wore no head cover, scalp cooling results were

Table 1 Patient and scalp cooling characteristics of patients admissible for evaluation of CIA status, with and without scalp cooling (n=144)

	No scalp cooling (n=15) (%)	Scalp-cooled, 90-min PICT (n=53) (%)	Scalp-cooled randomisation		
			90-min PICT (n=38) (%)	45-min PICT (n=38) (%)	p value
Total number of patients included (n=188)	20	65	50	53	
Unsuitable/CIA status unknown (n=44)	5	12	12	15	
Suitable/CIA status known (n=144)	15	53	38	38	
Age (mean)	61	56	61	61	0.9
Gender					0.6
Male	6 (40)	12 (23)	17 (45)	19 (50)	
Female	9 (60)	41 (67)	21 (55)	19 (50)	
Cancer					0.3
Breast	9 (60)	29 (55)	18 (47)	14 (37)	
Prostate	5 (33)	9 (17)	14 (37)	11 (29)	
Lung	1 (7)	10 (19)	5 (13)	12 (31)	
Ovary	0	4 (8)	1 (3)	1 (3)	
Gastrointestinal/Colorectal	0	1 (2)	0	0	
Chemotherapy Docetaxel					0.5
Monotherapy	10 (67)	38 (72)	29 (76)	26 (68)	
Carboplatin	0	9 (17)	5 (13)	9 (24)	
Herceptin	3 (20)	4 (8)	4 (11)	3 (8)	
Doxorubicin (Myocet)	1 (7)	1 (2)	0	0	
Capecitabin (Xeloda)	1 (7)	1 (2)	0	0	
Dosage Docetaxel					0.8
75 mg/m^2	11 (73)	29 (55)	23 (61)	22 (58)	
100 mg/m^2	4 (27)	24 (45)	15 (39)	16 (42)	
Cumulative dosage (mean)	Unknown	447	428	470	0.5
Chemotherapy setting					0.08
Adjuvant	0	4 (8)	2 (5)	7 (18)	
Palliative	15 (100)	49 (92)	36 (95)	31 (82)	
Median pre-cooling time[a] (min) (min–max)	–	35 (10–140)	30 (0–125)	30 (15–100)	1.0
Median PICT (min) (min–max)	–	90 (5–155)	90 (15–150)	45 (25–165)	<0.0001
Median number of cooling sessions, in patients not wearing a wig or head cover (min–max)	–	6 (2–18)	6 (2–10)	6 (2–15)	0.8
Median number of cooling sessions, in patients wearing a wig or head cover (min–max)	–	3.5 (1–8)	2.5 (1–6)	3.5 (1–6)	1.0

PICT post-infusion cooling time, *min* minutes, *min–max* minimal–maximal

[a] Median of all cooling sessions, multiple sessions per patient possible

evaluated after a median of six chemotherapy cycles. The median PICTs conform to the protocol. However, some deviations of the planned cooling times occurred after randomisation: in the 45-min PICT group, three patients had a median PICT longer than 55 min (range 58–68) versus three patients with a median below 80 min (range 45–53) in the 90-min PICT group. All these six patients were analysed in the assigned group and ultimately wore no wig or head cover. Patient characteristics did not significantly differ between both randomised groups (except median PICT).

In the observational part of the study, 90-min PICT resulted in 81 % of the 53 patients not requiring a wig or head cover (Table 2) compared to 27 % of the 15 non-scalp-cooled patients (p<0.0001). In the randomised part of the study, 90-min PICT resulted in 79 % of the 38 patients not requiring a wig versus 95 % of the 38 patients with 45 min PICT (p=0.04). In 11 patients in whom the pre-infusion cooling time was at least once ≤20 min (range 0–20 min) and in 14 patients with at least once a shorter post-infusion cooling time than planned (range 5–30 min), all but one patient wore no wig or head cover.

Table 2 Use of wig or head cover in scalp-cooled patients with different PICTs

	PICT (min)	*n*	% no wig or head cover
Observational	90	53	81
Randomised	90	38	79*
	45	38	95*

*p=0.04 (90 vs 45 min)

Results did not differ between docetaxel monotherapy and combinations of docetaxel with carboplatin, trastuzumab, doxorubicin or capecitabin (p=0.4). Only two of the 54 males reported to wear a wig or head cover, both had no scalp cooling. All but two males in the 45-min PICT group had a docetaxel dose of 75 mg/m^2. Overall, 65 % of the scalp-cooled female patients had a dose of 100 mg/m^2.

A VAS for tolerance was performed 632 times, resulting in a mean score of 79 (SD 20, range 0–100), regardless if the patient was admissible for evaluation of hair preservation. Information about headaches was reported 645 times: in 512 (80 %) sessions, patients reported no headache; in 86 (13 %), minimal; in 29 (4 %), moderate; and in 18 (3 %) sessions, patients reported severe headaches. Furthermore, no side effects were reported, with the exception of one patient who had cold sensations.

Follow-up of scalp-cooled patients was completed in May 2010. At that time, 65 % of the patients (n=129) were deceased. With an overall median follow-up of 17 months after completion of chemotherapy, no scalp metastases were reported.

Among patients of whom CIA status was known (n=129), 115 stopped scalp cooling as their chemotherapy treatment was completed, ten patients stopped because of severe CIA, one patient due to intolerance and three patients died in the period they received chemotherapy.

Out of 39 scalp-cooled patients in whom CIA status was unknown, six stopped scalp cooling due to intolerance during the first chemotherapy cycle. Other reasons for missing CIA status were as follows: stopping chemotherapy before completing the second cycle (n=10), deceased before hair loss could be assessed (n=3), questionnaires lost at the day care unit (n=7), scalp cooling was stopped due to detection of a scalp skin metastasis after the first chemotherapy treatment (n=1) or various other reasons (n=12).

Discussion

This study showed a significant advantageous result of scalp cooling in patients randomised for a PICT of 45 min compared to a PICT of 90 min. These patients were treated with 3-weekly docetaxel-containing chemotherapy, administered in 60 min, with or without other cytotoxic drugs. The very good hair preservation, where 79–95 % of scalp-cooled patients receiving docetaxel (75–100 mg/m^2) wore no head cover, is in accordance with the results reported in other studies with docetaxel as single agent or in certain combinations (83–100 %) [3–9]. As long as no clinically feasible method is available to measure hair preservation objectively, the best approach of measuring the satisfaction with scalp cooling is, in our opinion, whether patients use a wig or head cover.

Reducing the PICT to 45 min was not an expected course because a review showed a general trend in favour of a longer PICT: “the longer, the better” [1]. However, in Breed’s review, PICTs were compared for many chemotherapy types and dosages. Better results of a short versus a long PICT may be explained by a decreased exposure time of hair follicles to toxic drugs. Longer PICTs may delay the efflux of cytotoxic agents from the hair follicle cells to the blood stream at the time blood concentrations of cytotoxics decrease. Moreover, repair mechanisms of hair root cells may be inhibited for a longer time by the low temperature if there is an unnecessary long PICT. This hypothesis is to some extent supported by the preservation of hair in each of the 14 patients in this study who had at least once a very short PICT (≤30 min) due to protocol deviation.

The tolerance of scalp cooling was very high (VAS=79), and no headaches were reported in the majority of the scalp cooling sessions. Only 5 % of the patients stopped scalp cooling due to intolerance, which is comparable with the literature [1].

In this study, 37 % of scalp-cooled patients were males, indicating that they also value their hair important, as confirmed by the literature [13–15]. Scalp cooling should regularly be offered to them too. None of the scalp-cooled males used a wig or head cover partly because scalp cooling results are better in lower docetaxel dosages (75 mg/m^2) [27]. Besides, some of them might not have felt the need for a head covering when CIA ultimately occurred. Therefore, the efficacy of scalp cooling in this study may be somewhat overestimated. The significant advantage of 45-min PICT remains because of equal division of gender and dosages in both randomised groups.

Scalp cooling was effective, but the exact quantitative advantage of scalp cooling regarding hair preservation in docetaxel-treated patients is still unknown, while too few non-scalp-cooled patients were included, and no reliable data from other non-scalp cooling studies are available. In phase II and III clinical trials of 3-weekly docetaxel monotherapy regimens of 100 mg/m^2, the incidence of CIA differed from 42 % (grade 1–4) of the patients in one study to 100 % (only grade 2+3) of the patients in another study

[16–23]. For docetaxel of 75 mg/m^2 monotherapy or combined with cisplatin or carboplatin or capecitabine, CIA was reported in 40–89 % of the patients [19, 24–26]. Efficacy of scalp cooling has been proven in six out of seven randomised studies that compared scalp-cooled with non-scalp-cooled patients [2].

To routinely use a 45-min PICT at present may only carefully be justified in patients who are treated with docetaxel monotherapy or the combinations used in our study. Confirmation of our findings in a larger cohort of patients is certainly warranted. Further implementation of scalp cooling devices and improvement of the results can only be successful if national, preferably international, standardization is achieved.

Conclusion

This study showed very good results and tolerance of scalp cooling in 3-weekly docetaxel-containing chemotherapy regimens. A 45-min PICT is advantageous for the patients, as staying longer than necessary in the hospital while receiving chemotherapy is often a reason for rejecting scalp cooling. Time investment is frequently considered a reason for not introducing scalp cooling in a hospital or for offering it only to a restricted patient group. Patients (women and men) who are treated with docetaxel-containing regimens, except combined with doxorubicin and cyclophosphamide (TAC), should be informed on the protective effect and high tolerability of scalp cooling in avoiding CIA.

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Conflict of interest None declared.

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