Clinical aspects of scalp cooling in chemotherapy induced alopecia

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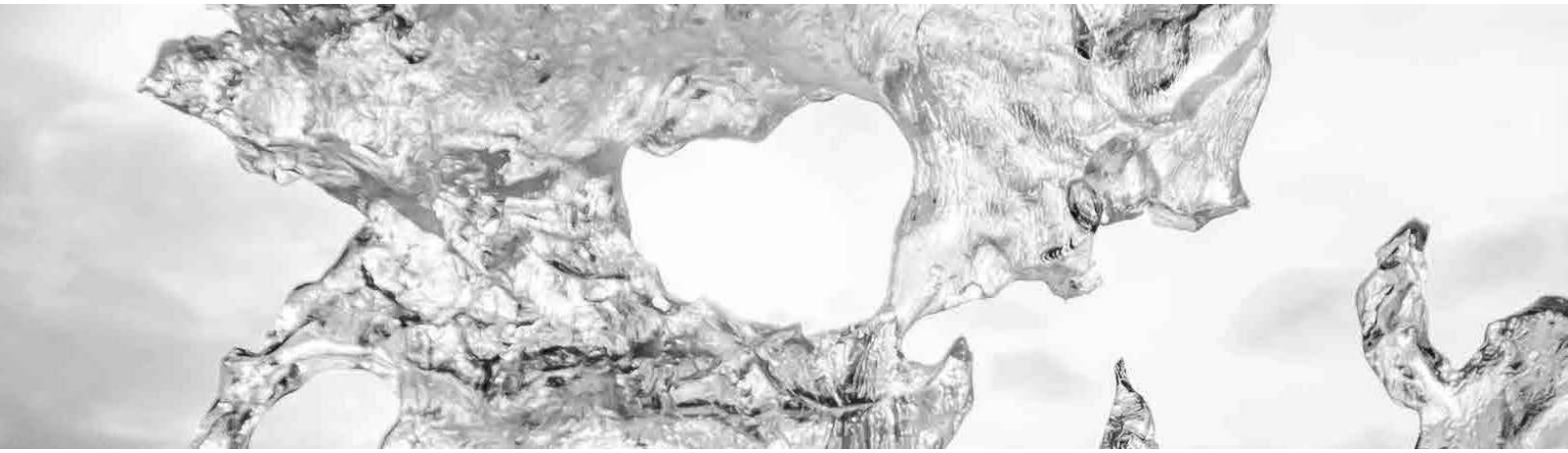
Chapter 2



Factors influencing the effectiveness of scalp cooling in the prevention of chemotherapy-induced alopecia

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ABSTRACT

Introduction: The success of scalp cooling in preventing or reducing chemotherapy induced alopecia (CIA) is highly variable between patients and chemotherapy regimens. The outcome of hair preservation is often unpredictable and depends on various factors.

Methods: We performed a structured search of literature published from 1970 till February 2012 for articles which reported on factors influencing the effectiveness of scalp cooling to prevent CIA in cancer patients.

Results: Literature search identified 192 reports of which 32 studies were considered relevant. Randomised studies on scalp cooling are scarce and there is hardly information on the determinants of the result. Hair preserving results of scalp cooling depend at least on dose and type of chemotherapy, with less favourable results at higher doses. Temperature seems to be an important determinant. Various studies suggest that a subcutaneous scalp temperature below 22°C is required for hair preservation.

Conclusions: The hair preserving results of scalp cooling are variable and mainly depend on type and dose of chemotherapy and probably on degree and duration of cooling.

INTRODUCTION

Chemotherapy induced alopecia (CIA), although being reversible, is for patients one of the most distressing side-effects. It has psycho-social implications and may affect body image and acceptance of treatment.(1-5) For some patients CIA is a reason to refuse chemotherapy, and up to 8% of patients may choose less effective chemotherapy regimens if these regimens do not cause hair loss.(6;7)

In healthy persons, scalp hair follicles show a pattern of cyclic activity. The hair growth (anagen) phase involves the growth of a hair from a hair follicle and lasts for three to seven years. During the transitional (catagen) phase, the hair follicle atrophies and migrates upwards to a resting level in the skin. During the resting (telogen) phase, the hair does not grow but stays attached to the hair follicle. The telogen phase ends when the old hair is shed and a new hair is regenerated in the anagen phase. In the adult scalp, approximately 90% of the follicles is in the growth phase.(8;9)

Chemotherapy acts on rapidly growing cells including hair follicles and chemotherapy induced shedding of hairs usually occurs seven to fourteen days after infusion.(8;10) The incidence and severity of alopecia depends both on the type (table 1) as well as the dose of chemotherapy.(6;9;11-13) Apart from hair loss from the scalp, patients may also loose their eyebrows, eyelashes and pubic hair after several cycles of chemotherapy. Although alopecia is a reversible side effect, permanent alopecia has been reported incidentally after high dose chemotherapy.(10)

Table 1. Cytotoxic drugs that cause chemotherapy induced alopecia

Mild alopecia (0,1-1%)	**Moderate alopecia (1-10%)**	**Severe alopecia (>10%)**
Bortezomib	Bleomycin	Busulfan
Cabazitaxel	Cyclophosphamide	Docetaxel
Carboplatine	Epirubicin	Doxorubicin
Catumaxumab	Trastuzumab	Etoposide
Cisplatin	Panitumumab	Gemcitabine
Cytarabin		Idarubicin
Dactinomycin		Ifosfamide
Ixabepilone		Irinotecan
Lomustine		Mitomycine
Methotrexaat		Oxaliplatin
Pemetrexed		Paclitaxel
		Topotecan
		Vinorelbine
		Procarbazine

Source: Investigator brochures

Since the 1970s, scalp cooling is being used to reduce and prevent CIA.(14) It reduces skin temperature, thereby affecting the exposure and metabolism of cytotoxic agents in the hair follicles. However, the effectiveness of scalp cooling in preventing alopecia is highly variable and unpredictable. We therefore wanted to explore possible reasons why scalp cooling works in one patient but fails in another.

MATERIALS AND METHODS

We designed a search strategy to identify relevant literature that described the use of scalp cooling in preventing chemotherapy induced hair loss among patients treated for cancer. We performed our search on February 24, 2012 in the electronic databases PubMed, Embase, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) for literature published from 1970 through February 24, 2012, linking the subject search headings with text word and MESH terms.

A combination of the following search terms was used: ((("chemotherapy"[all fields] OR "antineoplastic protocols"[Mesh] OR "antineoplastic agents"[Mesh] OR "neoplasms/drug therapy"[Mesh Terms] OR "chemotherapy-induced"[all fields]) AND ("hair loss"[all fields] OR "alopecia"[Mesh] OR "alopecia"[all fields])) OR "alopecia/chemically induced"[Mesh Terms]) AND ("scalp cooling"[all fields] OR "scalp hypothermia" OR "cold cap"[all fields] OR ("hypothermia, induced"[Mesh] AND ("scalp"[Mesh] OR "scalp"[all fields])))

We did not restrict the search strategy to a particular type of study design.

Articles were selected if they assessed any possible factors affecting the effectiveness of scalp cooling in preventing alopecia after chemotherapy. Only full text articles in English and Dutch were considered. We also did a manual search for any relevant references used in the articles found. Papers that described scalp cooling as a safety issue or focussed solely on impact or tolerance were excluded.

RESULTS

The initial search resulted in a total of 192 citations (76 Hits in PubMed, 92 in Embase, and 24 in CINAHL). After removing duplicates, 102 citations remained; 70 were discarded based on title or abstract because they did not meet the inclusion criteria and the 32 citations that were considered relevant, were included in this review (table 2). A manual search of references in the relevant articles did not yield any additional study. The majority of the articles (20 out of 32) was published between 1980 and 2000. Since 2010, only 3 articles have been published on possible factors influencing the effectiveness of scalp cooling in the prevention of CIA. Excluding one large multicenter observational study (ref 14), the median number of reported patients was 35 (range 9-180).

Table 2. Factors influencing the result of chemotherapy induced alopecia

	Author	Year	N of patients	Patient charateristics	Chemotherapy characteristics	Scalp cooling characteristics	Scalp cooling techniques
1	Anderson	1981	31			X	
2	Hunt	1982	22		X	X	X
3	Guy	1982	12				X
4	Gregory	1982	24			X	
5	Dean	1983	33			X	X
6	Wheelock	1984	11		X	X	
7	Satterwhite	1984	26		X	X	
8	Vendelbo	1985	61			X	
9	Middleton	1985	60			X	X
10	Bulow	1985	10			X	
11	Symonds	1986	26			X	X
12	Robinson	1987	32			X	
13	David	1987	180			X	
14	Giaccone	1988	39		X		
15	Hillen	1990	48			X	X
16	Adams	1992	34		X	X	
17	Tollenaar	1994	35		X	X	
18	Lemenager	1997	98		X	X	X
19	Peck	2000	10				X
20	Katsimbri	2000	70			X	X
21	Christodoulou	2002	83			X	X
22	Ridderheim	2003	74			X	X
23	Macduff	2003	40			X	X
24	Massey	2004	94			X	
25	Grevelman	2005	Review			X	
26	Janssen	2005	Model	X		X	
27	Janssen	2007	9			X	
28	Auvinen	2010	64		X	X	
29	Komen	2011	27			X	
30	Kargar	2011	63			X	X
31	Van den Hurk	2012	76			X	
32	Van den Hurk	2012	1411	X	X		X

The effectiveness of scalp cooling in cancer patients depends on many factors, which can be related to patient characteristics, chemotherapy characteristics and the procedure of scalp cooling (table 2). Only one study reported on a relationship between patient characteristics and scalp cooling effectiveness, while in 9 articles various chemotherapy schedules were tested and in 31 articles technical aspects of scalp cooling were described.

Patient characteristics

In a large multicenter observational study in the Netherlands Van den Hurk et al.(15) concluded that scalp cooling was more effective at younger age, in male patients and in patients with a Caucasian type of hair. In a computer model study, Janssen et al.(16) found that the thickness of the hair layer correlated with the scalp skin temperature during scalp cooling. This may explain the lower effectiveness of scalp cooling in patients with Afro hair, who have a thick layer of hair which acts as an insulating layer between the cooling cap and the scalp.

Chemotherapy characteristics

Type and dose

The incidence and severity of CIA using scalp cooling depends on the type and dose of chemotherapy.(1;1;2;12;15;17-22) Only three of these reported studies randomised patients to chemotherapy either with or without scalp cooling. Therefore, results of effectiveness of scalp cooling have to be compared with historical series with identical chemotherapy regimens. An ongoing Dutch observational study collects data on the effectiveness of scalp cooling with various types and doses of chemotherapy regimens (table 3)(15) For anthracycline containing regimens, a higher dose of anthracycline was correlated with a worse outcome of scalp cooling. (15;17) With 5-Fluorouracil-Epirubicin-Cyclophosphamide (FEC) chemotherapy, 33% of the patients treated with epirubicin at a dose of 100 mg/m^2 did not require a head cover versus 52% of the patients treated with epirubicin at a dose of 90 mg/m^2. Likewise, 59% of the patients treated with docetaxel at a dose of 100 mg/m^2 did not require a head cover versus 79% of the patients treated at a dose of 75 mg/m^2 (table 3).(15) Of notice, scalp cooling failed to prevent alopecia in most patients who were treated with the combination of docetaxel, adriamycin, cyclophosphamide (TAC) chemotherapy for early breast cancer.

Table 3. Overview of scalp cooling results in The Netherlands 2006-2009

Indication and chemotherapy type[1]	Total number of patients using scalp cooling	% patients not wearing a wig or head cover
Breast cancer		
FEC-T (500/100/500-100)[2]	45	47
FEC (500/100/500)	123	33
FEC (500/90/500)	552	52
FAC (500/50/500)	38	55
P (70-90) (mono/combinations)[3]	39	82
T (100) (mono/combinations)[4]	42	59
T (75) (mono/combinations)[4]	58	79
TAC (75/50/500)[5]	66	8
AC-TH (60/600-100)[2]	16	63
AC-PH (60/600-175)	21	29
AC-PH (60/600-80)	29	48
AC (60/600)	74	39
Ovarian cancer		
P-Carbo(175-5/6)	49	37
Colon cancer		
Irinotecan (350)	41	29

[1]Dosage in mg/m^2

[2]Sequentially: FEC followed by T/ AC followed by T or P and H

[3]Weekly schedule

[4]Docetaxel combinatons with exception of docetaxel/adriamycine/cyclofosfamide (TAC)

[5]T,A en C simultaneously

C: Cyclofosfamide; Carbo: Carboplatin; A: Adriamycine; T: Docetaxel; E: Epirubicine; F: 5-fluorouracil; H: Herceptin (trastuzumab); P: Paclitaxel

Source: Breed W, van den Hurk CJ, Peerbooms M. Presentation, impact and prevention of chemotherapy induced hair loss: scalp cooling potentials and limitations: *dermatology* 2011; 6: 109-125

Liver function

According to several studies, scalp cooling does not prevent CIA in most patients with biochemical evidence of abnormal liver function.(2;23-27) This may be predicted on the basis of pharmacokinetics of chemotherapy that is metabolized by the liver. For these drugs, an impaired liver function is associated with higher and more prolonged plasma concentrations.(23) In contrast, Grevelman et al.(11) concluded that in only six out of 13 studies, impaired liver function seemed to be related to less benefit from scalp cooling.(11) In these studies patients were treated with doxorubicin or epirubicin.

Scalp cooling characteristics

Temperature

It is evident that optimal fitting of the cold cap is an important factor for success. Bald areas are seen where the cap did not fit properly (figure 1). Contact between the cold cap and the scalp skin is decisive for lowering the skin temperature.(16) In 1982, Gregory et al.(28) found a relation between the degree of decrease in scalp skin temperature and the protective effect of scalp cooling against hair Ioss in patients treated with doxorubicin. They concluded that to prevent CIA the subcutaneous scalp skin temperature should be reduced below 22ºC corresponding to an epicutaneous scalp temperature below 19ºC to prevent CIA .(29) Hillen et al.(30) attributed the success of their air-cooling methods in part to achieving epicutaneous scalp temperatures below 15ºC and Bülow reported that in two out of ten healthy volunteers it was impossible to obtain a subcutaneous scalp temperature below 28ºC, which is in agreement with the findings of Gregory and Janssen and implies that some persons consistently respond to scalp cooling with only a minor reduction in subcutaneous temperature.(28;29;31) As these studies used different and obsolete scalp cooling techniques and report different cut-off levels of scalp skin temperature, a study on scalp temperature using the modern Paxman® system is presently being done at our centre. Janssen demonstrated that wetting the hair increased the conductivity of the hair layer, resulting in a further decrease in scalp skin temperature.(16) However, there are no randomized studies regarding the influence of wetting on scalp skin temperature and scalp cooling success rates, while wetting the hair increases the burden for the patient.

Figure 1. Bald areas are seen where the cold cap did not fit properly

Perfusion

To gain more insight into the effect of cooling, Janssen et al. studied the relationship between skin temperature and skin perfusion during a cooling experiment in 9 healthy subjects.(16) During scalp cooling, relative perfusion of the scalp skin gradually dropped

down to 28%. A plateau in perfusion was reached after prolonged cooling to lower skin temperatures. This reduction in perfusion was in line with the findings of Bülow(29) and Hillen(30), who found that blood flow during scalp cooling was reduced to 25% of the basal value. Bülow also stated that blood flow was not reduced any further when the subcutaneous scalp temperature was below 30ºC.(29)

Scalp cooling time

The duration of scalp cooling might influence the hair protective effect of scalp cooling. In most studies the pre-cooling time (time between start of scalp cooling and start of intravenous infusion of chemotherapy) ranged from 5 to 30 minutes.(12;17-23;25-27;30;32-37) At the Medical Centre Alkmaar we have measured serial scalp skin temperatures during scalp cooling in healthy subjects and patients to determine the optimal pre-infusion cooling time. In 27 persons treated with scalp cooling using the Paxman® PSC1 system, scalp temperature reached a constant level of approximately 18ºC after 45 minutes. These preliminary data suggest that as no further reduction in temperature occurred, a pre-infusion cooling time of 45 minutes seems optimal when a non pre-cooled cap is used.(38)

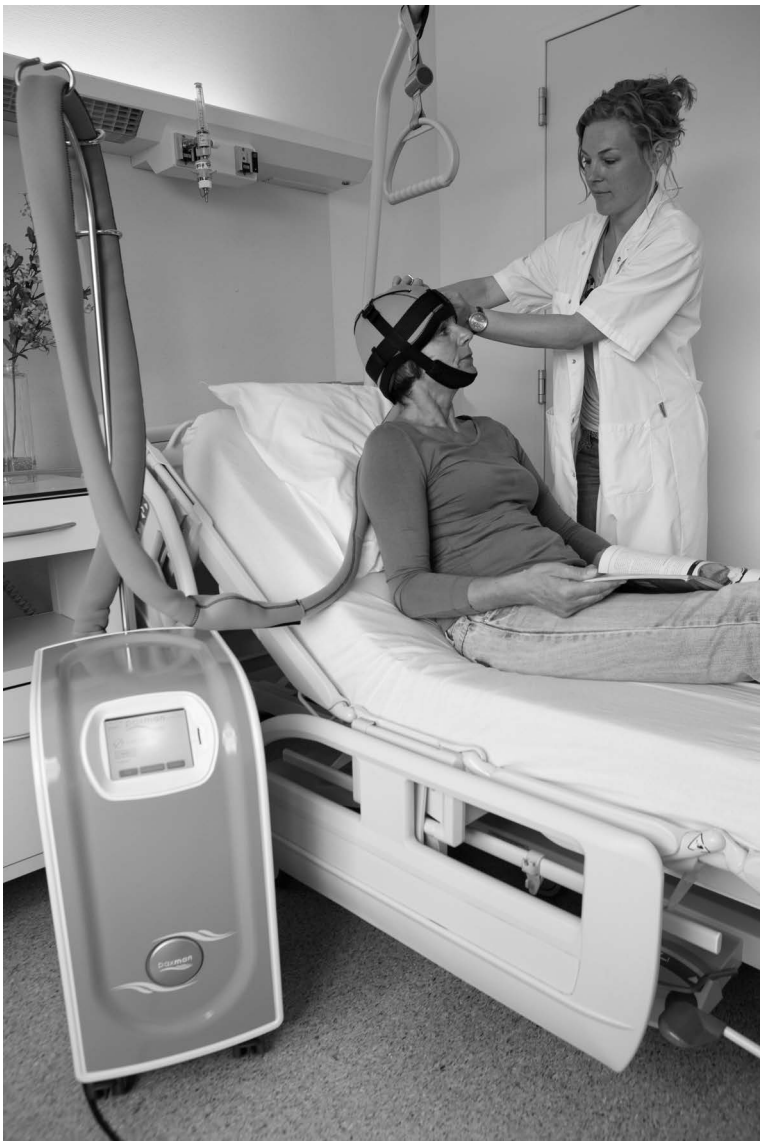
While the pre-infusion cooling time is well known, there is much uncertainty about the post-infusion cooling time. Theoretically, the cooling period after infusion of chemotherapy should be related to pharmacokinetics of exposure to the cytostatic agent and its active metabolites.(11;22) However, research on post infusion cooling time is very scarce. In daily practice, post-infusion cooling times range from 15 minutes to 4 hours.(12;17-23;25-28;30;32;34-37) A study comparing the effect of a shorter post-infusion time in patients treated with docetaxel (90 versus 45 minutes) showed no difference in results on hair preservation (95% versus 79% did not need head covering).(39) Therefore, a new docetaxel study has started in which patients are randomized between 45 versus 20 minutes of post-infusion cooling time. In contrast, in breast cancer patients treated with adjuvant FEC chemotherapy for which scalp cooling is less effective (about 50% no head covering), it is investigated whether prolonging the post-infusion cooling time to 150 minutes is favorable over 90 minutes.

Scalp cooling techniques

Several techniques have been used to induce hypothermia: chilled air, bags with crushed ice, frozen cryogel packs or packs with an endothermic cooling reaction, special caps with cryogel and an insulation layer, and caps connected to a cooling device using air or fluid as a medium and equipped with a thermostat.(2;12;18;20;26;30;32-37;40;41) Few studies compared the effectiveness of different methods of scalp cooling.(30;32;34) Dean et al compared a Kold Kap® device with ice packs in the treatment of 62 patients

with doxorubicin.(34) Sixty-three percent of Kold Kap® patients and 56% of ice pack patients did not require wigs. Although cooling devices using air or fluid as a medium and equipped with a thermostat (figure 2) provide more constant cooling that can be maintained for longer, there is no conclusive evidence that permanently cooled caps give better hair preservation. Studies comparing skin temperatures and skin perfusion as obtained with various methods of scalp cooling are lacking. Although bags with ice as well as special caps are both well tolerated, caps are lighter in weight and easier to apply, which might offer a comfort advantage.

Figure 2. Cooling device equipped with a thermostat



Side effects and contraindications of scalp cooling

Scalp cooling is generally well tolerated.(2;3;11;42) Results obtained from patients appear to indicate high levels of comfort and acceptability with evidence of only minor and reversible side-effects.(1) The most often reported side-effects of scalp cooling are:

headaches, complaints of coldness and/or uncomfortable sensations and among others claustrophobia.(11;20;42) Scalp cooling is contra-indicated in cases of cold sensitivity, cold agglutin disease, cryoglobulinemia, cryofibrinogenemia and post-traumatic cold dystrophy.(11) Scalp metastases have rarely been reported in the literature but caution regarding its development has been a limitation for the broad-scale application of scalp cooling during chemotherapy.(6;43) Theoretically, tumour cells that have seeded in the scalp might not receive adequate chemotherapy during hypothermia allowing them to grow at a later date.(6) Since various studies have reported recently on the safety of scalp cooling (44;45), a feasibility studies on scalp cooling in oncology patients have recently started in the United states.

DISCUSSION

While the incidence and severity of alopecia as a side effect of chemotherapy depends on the type and dose of chemotherapy(6;9;11-13), the outcome of hair preservation by scalp cooling is often unpredictable and varies between patients. The effectiveness of scalp cooling to prevent CIA depends on various factors such as patient characteristics, chemotherapy characteristics and scalp cooling characteristics. Unfortunately, there are hardly any randomized studies on the effectiveness and safety of scalp cooling in CIA. Only few studies have investigated which patient characteristics could be of influence and which method of scalp cooling is the most effective. In this review we found that scalp cooling results are better with certain chemotherapy types (taxanes). Results are less favourable at higher doses of chemotherapy. Skin temperature seems to play an important role, but until now, there is no evidence for a cut-off point under which alopecia can be prevented by scalp cooling. There are suggestions in the literature that a subcutaneous scalp temperature below 22°C is required for hair preservation, but as these studies on temperature used different and obsolete scalp cooling techniques, there is no conclusive evidence so far. Ideally scalp cooling should be applied more patient tailored. If a threshold level of scalp temperature is to be a critical issue, timing and technique of scalp cooling should be adapted to individual measurements of skin temperature. To advise patients on an individual basis on scalp cooling in preventing CIA, factors like optimal temperature and post-infusion cooling time should be investigated further. At present, various hospitals in Europe, Canada and Japan are already using scalp cooling routinely.

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