Review

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Prevention of chemotherapy-induced hair loss by scalp cooling

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Background: Chemotherapy-induced temporary hair loss is one of the most common and distressing side-effects of cancer therapy. Scalp cooling to reduce this hair loss is a controversial issue for many doctors and nurses. This may be due to inadequate knowledge.

Methods: This review from 53 publications and three personal communications focuses on the efficacy of the treatment, side-effects, possible disadvantages and the controversies in these areas.

Results: Scalp cooling has become an increasingly effective method to prevent hair loss, especially when anthracyclines or taxanes are used. Unfortunately, many studies were small and badly designed and are therefore difficult to compare. There is a considerable variation in the success rates in the various studies. This remains unexplained, but the cooling time, the chemotherapy used and the temperature seem to be influential. Scalp cooling should not be used if chemotherapy is given with a curative intent in patients with generalised haematogenic metastases. The majority of patients tolerate cooling very well.

Conclusion: Scalp cooling is effective but not for all chemotherapy patients. Further psychological, clinical and biophysical research is needed to determine exact indications for cooling and to improve the effect, tolerance, side-effects and the cooling procedure. Multicentre trials should be carried out to gather this information.

Key words: alopecia, chemotherapy-induced hair loss, cold cap, hair preservation, hypothermia, scalp cooling

Introduction

Chemotherapy-induced temporary hair loss is one of the most common and emotionally distressing side-effects of cancer therapy [1–3]. Since about 1970, many preventive measures have been tried to reduce chemotherapy-induced alopecia: the tourniquet [4], medicaments [5] and scalp cooling. Currently, preventive measures mainly focus on scalp cooling. This is done either by procedures in which the cooling agent (ice cap, or gel cap) must be changed several times or by continuous cooling of the scalp with cold air or cold liquid. There are two scientific rationales for scalp cooling. The first is vasoconstriction, which reduces the blood flow to the hair follicles during peak plasma concentrations of the chemotherapeutic agents and so reduces cellular uptake of these agents. This was demonstrated by Bülow et al. [6]. The second rationale is reduced biochemical activity, which makes hair follicles less susceptible to the damage of chemotherapeutic agents. The latter may be more important than vasoconstriction [6]. A lower glucose/lactate was demonstrated in a hypothermic scalp than in the normothermic scalp [7].

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This review of literature will focus on the following areas: the efficacy of the treatment, side-effects, possible disadvantages and the controversies in these areas.

Results

Between 1973 and 2003, 53 publications and three personal communications were found reporting cooling results in more than one patient, partially in nursing journals. Seven trials were randomised and 49 were non-randomised. In 14 of the non-randomised studies, the results were compared with a (historical) control group. The type of treatment was adjuvant in seven studies, palliative in nine, both adjuvant and palliative in 12, and unknown in the remaining 28 studies. Most studies were carried out in Europe, 11 took place outside Europe. The number of patients varied from six to 180. There was a great variation in chemotherapeutic regimens and cooling methods. The latter varied from ice packs to gel caps or cooling machines. Methods used to evaluate hair loss also varied considerably.

Results of hair preservation

In six out of the seven randomised studies, a significant advantage was seen when scalp cooling was used (Table 1).

Table 1. Results of randomised studies

Reference	No. of cooled patients	No. of controls	Chemotherapy agents and doses (mg/m^2)	% patients with good[a] hair preservation (controls)	*P* value
[8]	40	37	D50, Vc2[b], F500, 4× p.o.: M20 + Ch40	50% (19%)	$P < 0.05$
[9]	19	16	Combinations including D30-70	37% (0%)	$P < 0.025$
[10]	10	9	D31-125[b], C300–800[b]	10% (0%)	NS
[11]	15	15	E75, DT75	25% (0%)	$P = 0.001–0.012$[c]
[12]	6	6	C600, M40, F600	100% (17%)	$P < 0.01$
[13]	19	16	C600, M40, F600	85% (63%)	$P = 0.014$[d]
[14]	12	13	D20-60 multiple combinations	75% (8%)	$P = 0.0009$

[a]WHO grade 0, 1, 2 unless in the opinion of the authors the hair preservation in a part of the patients with grade 2 is not good or if the authors mention 'good hair preservation', or 'no wig required'.
[b]Doses not per m^2.
[c]Depending on who rated hair loss: patients, nurses or experts.
[d]*P* value calculated for the incidence of alopecia of any grade.
C, cyclophosphamide; Ch, chlorambucil; Cp, cisplatin; D, doxorubicin; DT, docetaxel; E, epirubicin; F, 5-fluorouracil; M, methotrexate; Vc, vincristine; NS, not significant; p.o., orally.

In 13 out of the 14 non-randomised studies with historical control groups, the authors concluded positive results of scalp cooling for certain indications (Tables 2 and 3). The 35 studies without historic controls showed 31 positive results (Tables 2 and 3).

The 19 non-randomised studies carried out from 1995 onwards all showed positive results; five of these had (historical) controls (Table 2). The only randomised study carried out after 1995 showed (marginal) positive results with epirubicin and docetaxel.

The average success rate of the studies carried out before 1995 was 56% and from 1995 onwards 73% (Table 4).

In studies reporting results of several chemotherapy schedules (e.g. Refs [18, 27, 28, 34, 43]), their mean results were used to calculate the mean and median values in Tables 4 and 5.

The cooling time seems to influence the success rate of the studies. The median success rate was 76% if, after infusion of cytostatics, the cooling time was 90 min or more. When shorter post-infusion cooling times were used, the median success rate was 71% (Table 5). In the past few years, longer post-infusion cooling times have been used. Before 1995, post-infusion cooling for more than 90 min was used in only two out of 32 studies, whereas since 1995 this was the case in nine out of 20 studies. (In four studies the post-infusion cooling time was not specified.)

In 13 studies, liver function or the presence of liver metastasis were taken into consideration for the hair protective effect of scalp cooling. In six out of these 13 studies, impaired liver function seemed to be related to less benefit from cooling [10, 29, 35, 50, 52, 54].

Side-effects. The most often reported side-effects were: headaches, complaints of coldness and/or uncomfortable sensations, among others claustrophobia. These side-effects were in general not serious. There were a few studies in which in more than 10% of the patients side-effects were a reason for stopping the cooling procedure [9, 18, 31, 32]. Dougherty even reported that in the group of patients in which cooling had been ineffective, 38% of those patients felt they would want the scalp cooling procedure if they needed another chemotherapeutic treatment [1].

Scalp cooling is contra-indicated in cases of cold sensitivity, cold agglutinin disease, cryoglobulinemia and cryofibrinogenemia.

Long-term adverse consequences?

Scalp metastases. In only 24 out of 58 studies (including the two studies with only one patient), was attention paid to the presence of scalp skin metastases after cooling. Sixteen of those 24 studies mentioned explicitly that no scalp skin metastases were found. In six studies, scalp skin metastases were found in nine patients out of a total of about 2500 patients in the 56 studies [14, 23, 46, 48, 54, 57, 58]. Both Witman et al. and Forsberg had a patient (one with mycosis fungoides, one with leukaemia) in whom they thought there was a relation between the skin metastases and the cooling [57, 58]. Only Lemenager et al. [21] and Ridderheim et al. [25] looked systematically for the incidence of scalp skin metastases after cooling. In the 15 years that Lemenager et al. used scalp cooling, they did not find increased incidence in scalp metastases after cooling (median post-cooling follow-up of 9 months) [21]. Ridderheim et al. found no scalp metastases during a median follow-up period of 15 months among 74 patients [25].

One study even reported a decrease in size of a scalp skin metastasis despite cooling during chemotherapy [14].

Survival. No research has been carried out to evaluate the influence of scalp cooling on the survival time.

Discussion

Unfortunately, most articles on scalp cooling are of poor value and there are only seven randomised studies. Many studies are

Table 2. Results of non-randomised studies after 1994

Reference	No. of cooled patients	No. of controls	Chemotherapy agents and doses (mg/m^2)	Hairloss scoring[a]	% patients with good hair preservation (controls)
[15]	15		ANR, TX, CMF	Graded scale	80%
Personal communication: C. Christodoulou, Athens Medical Centre, Greece	83		D50-60 or E60-110 or P175-200 or ET and combinations	Graded scale	65%
[1]	30		D or E or in multiple combinations	Graded scale	50%
[16]	127		P180, DT80, D60, C500, M50 in multiple combinations	Graded scale	87%
[17]	23		D > 50, C with multiple combinations	Graded scale	90%
[18]	57		Multiple combinations	Graded scale	TX: 88%, ET: 100%, TX + ANR: 36%, ANR: 100%
Personal communication: A.D. Klaren, Albert Schweizer Hospital, Dordrecht, The Netherlands	23		D60, C600	No wig required	76%
[19]	31		D60, C600 or DT 100 or multiple combinations	No wig required	52%
Personal communication: B. Kolen, Elisabeth Hospital, Tilburg, The Netherlands	55		D60, C600 or multiple combinations	No wig required	47%
[20]	39	H	DT100	Graded scale	97% (5%)
[21]	98		DT100	Graded scale	86%
[2]	29	H	C E (min50) F	No wig required	50% (0%)
[7]	9	2	P135-175/DT100/and multiple combinations	Graded scale	100 (0%)
[22]	94		FEC60-75 and multiple combinations	Graded scale	89%
[23]	10	7	F600, E50, C600	No wig required	70% (0%)
[24]	27	109	Mi12, C600	Graded scale	41% (16%)
[25]	74		Multiple combinations	No wig required	78%
[26]	45		D or E > 50 and multiple combinations	Graded scale	82%
[27]	138		Multiple combinations	Graded scale	CMF: 100%, D: 54%, E: 95%, TX: 81%

[a]See Table 1.

ANR, anthracyclines; C, cyclophosphamide; Cp, cisplatin; Ct, cytarabine; D, doxorubicin; DT, docetaxel; E, epirubicin; ET, etoposide; F, 5-fluorouracil; M, methotrexate; Mi, mitoxantrone; P, paclitaxel; TX, taxanes; H, historical control group.

rather small or have no exact description of the duration of infusion and the method of scalp cooling. Although the 49 non-randomised studies lack an optimal control group, they give some relevant clinical information.

The original idea was to analyse the studies to find the relation between the temperature of the scalp obtained in the various studies and the effect of scalp cooling; however, temperature measurements were only done in one study.

Success rates

It is evident that cooling can prevent hair loss. However, it is very difficult to compare most studies, because of differences in patient characteristics, chemotherapy, cooling and hair loss assessment. This is demonstrated in hair preservation with similar CMF regimens in two randomised trials: 17% and 63% in controls.

The success of cooling is most apparent in the randomised studies (Table 1), but in a number of the 49 non-randomised studies, cooling also seems effective (Tables 2 and 3). Table 4 suggests better results from 1995 onwards than before that period, although this might be influenced by publication bias.

The wide variation in reported success rates is unexplained. The success of scalp cooling depends on many factors like type of cytostatics, the doses, the number of chemotherapy courses and the admission method [14, 28, 35, 49]. In particular, when anthracyclines or taxanes were used, the positive effect has been proven [7, 14, 21, 45]. If a combination of anthracyclines and taxanes were used, the results were

Table 3. Results of the non-randomised studies before 1995

Reference	No. of cooled patients	No. of controls	Chemotherapy agents and doses (mg/m^2)	Hair loss scoring[a]	% patients with good hair preservation (controls)
[28]	24		E100, E50	Graded scale	E100: 0%; E50: 86%
[29]	31		D40, Vc2 or Vd5	Graded scale	79%
[30]	88		C800-1000, M40-60 F200-250 and multiple combinations	Graded scale	90%
[31]	72	77	Multiple combinations	No wig required	72% (38%)
[32]	91		D, ±C	Graded scale + photos	61%
[33]	50		E30-50 (weekly)	Graded scale	100%
[34]	ns		D40	ns	55%
[35]	180		Multiple combinations	Graded scale	54%
[36]	33	H 120	D30, C150 ×4 p.o.	Graded scale + photos	60% (5%)
[37]	25	H 150	D30-40, C150–200 ×4 p.o.	Graded scale + photos	75% (5%)
[38]	13		D, Vc	ns	76%
[39]	6	5	D40, C1000, Vc1	Graded scale	0% (0%)
[40]	82		D30-70 alone or in multiple combinations	No wig required	57%
[41]	24	ns	D40, Vc2[b]	Graded scale	42% (5%)
[42]	12	H 100	D50, Vc1.4, C1000, M40	Graded scale + photos	100% (2%)
[43] (cold air)	48		Multiple combinations	Graded scale	CMFP: 95%; CMFPCAP: 30%, EC: 0%
[43] (cryogel)	13		Multiple combinations	Graded scale	CMFP: 89%; CMFPCAP: 0%
[44]	35		Combinations including D	Graded scale	100%
[45]	28		D40, Vc2, Vd5 or D80	Graded scale + photos	79%
[46]	176		Combinations including D	No wig required	58%
[47]	12	16	Combinations including D	Max % of hair loss	[b]
[48]	60		D40, Vc1.4, C200 ×4 p.o.	Graded scale	0%
[49]	47		ANR in multiple combinations	Graded scale	0%
[50]	22	10	E40-80	Graded scale	73% (20%)
[51]	37		D30, C200 ×4 p.o.	Graded scale	70%
[52]	26		D and multiple combinations	Graded scale	77%
[3]	32		D50, C1000 Vc1, 4, P40 ×5 p.o.	Graded scale	6%
[53]	35		C600, D50, F600	Graded scale	11%
[54]	61		C400, D25, F500	Graded scale	77%
[55]	18	18	Combinations including D	Graded scale	67% (17%)
[56]	11		D50, Cp50, C500, M20	Graded scale	0%

[a]See Table 1.

[b]The non-cooled patients lost an average of 80% of their hair; the cooled patients lost an average of 30% of their hair.

ANR, anthracyclines; C, cyclophosphamide; Cp, cisplatin; Ct, cytarabine; D, doxorubicin; Dr, daunorubicin; DT, docetaxel; E, epirubicin; ET, etoposide; F, 5-fluorouracil; M, methotrexate; Pr, prednisolone; Sem, semustine; Tg, thioguanin; TX, taxanes; Vc, vincristine; Vd, vindesine; H; historical control group; ns, not specified; p.o., oral.

considerably less positive [9, 14, 18]. As hair loss induced by paclitaxel is considerably increased if patients have undergone previous chemotherapy [59], it seems likely that the results of cooling will also be influenced by previous chemotherapy. Therefore previous chemotherapy treatments should always be taken into consideration when analysing results of scalp cooling.

Few studies have been made to find out which method of scalp cooling is the most effective [1, 13, 43]. Careful application of the cooling cap might be more important than the cooling system itself, as the contact between the cold cap and the scalp skin is decisive for scalp temperature as has been suggested in numerical modelling of scalp cooling [60].

Table 4. Results of studies before and since 1995

Reference	% patients with good hair preservation[a]		
	Mean value	Median value	Scatter
Studies before 1995 [3, 8–10, 12, 14, 28–46, 48–56]; 1563 cases	56	61	0–100
Studies since 1995 [1, 2, 7, 11, 13, 15–18, 20–27]; personal communication: C. Christodoulou, Athens Medical Centre, Greece; personal communication: A.D. Klaren, Albert Schweizer Hospital, Dordrecht, The Netherlands; personal communication: B. Kolen, Elisabeth Hospital, Tilburg, The Netherlands; [19][b]; 1047 cases	73	81	25–100

[a]See Table 1.

[b]The results of this study are not used for calculation of mean and median values as the patients are part of the Kolen study patients.

Table 5. Results of studies with various post-infusion cooling times

Reference	% patients with good hair preservation[a]		
	Mean value	Median value	Scatter
Post-infusion cooling time <90 min [1, 7–14, 17, 19–21, 25, 28–31, 33, 35–37, 39–52, 54–56]; personal communication: B. Kolen, Elisabeth Hospital, Tilburg, The Netherlands; [19][b]; 1864 cases	61	71	0–100
Post-infusion cooling time ≥90 min [2, 16, 18, 22, 23, 26, 27, 32, 53]; personal communication: C. Christodoulou, Athens Medical Centre, Greece; personal communication: A.D. Klaren, Albert Schweizer Hospital, Dordrecht, The Netherlands; 746 cases	69	76	11–89

[a]See Table 1.

[b]The results of this study are not used for calculation of mean and median values as the patients are part of the Kolen study patients.

Furthermore, the importance of the degree of hypothermia of the scalp skin has hardly been studied. In 1982, in a study with a limited number of patients, Gregory et al. found the best protective effect against hair loss in the group of patients with the lowest intradermal temperatures [41]. There have been no further studies to confirm this. Although accurate measurement of the scalp skin temperature during cooling is extremely difficult, temperature measurements or other parameters for skin temperature are necessary to determine the optimal hypothermia, pre-cooling times and optimal application of the cap.

Post-infusion cooling time also seems to be relevant for the results of cooling (Table 5). Theoretically, the cooling period after infusion of cytostatics should be related to the half-life time of the cytostatic used and their active metabolites but this is rarely done and has never been investigated [15, 53].

The importance of liver function to the success rate of scalp cooling is controversial. In six out of 13 studies with abnormal liver function or liver metastasis, less benefit from cooling was observed [29, 35, 45, 50, 52, 54].

Side-effects

Scalp skin cooling is generally well tolerated. Although side-effects are rarely a reason to stop the cooling, further research to improve tolerance for cooling might improve the results.

Long term adverse consequences?

In several publications, authors have been concerned about the possible protective effect of cooling on (micro-)metastases of the scalp skin [9, 12, 14, 25, 45]. Although the findings of Lemenager et al. and Ridderheim et al. seem to be very reassuring, one has to bear in mind that their conclusions were based on only a 9 month follow-up period [21, 25]. A good systematic study to look for the influence of cooling on scalp skin metastases and on survival time of patients would require very large numbers of patients and a long-term follow-up. It is clear that in the case of haematological malignancies with haematogenic metastases, cooling is contraindicated [57, 58]. Scalp cooling is controversial in patients with non-haematological malignancies who undergo chemotherapy with a curative intention.

Fear of undoing the effect of chemotherapy on (micro) brain metastases by cooling seems unrealistic as the current cooling techniques do not cause a significant decrease in brain temperature [60].

Recommendations

Based on the results of these studies, scalp cooling should be applied more. However, it is not possible to advise on the optimum application of the cooling methods (system, duration and temperature). Careful application of the cooling cap might

be more important than the cooling system itself. We recommend multicentre trials to study the optimal method, temperature and duration of cooling with various chemotherapy regimens. Patient satisfaction should be the most important criteria for success, because efforts to obtain objective measurements are very difficult and less important than the contentment of the patient.

Conclusions

Scalp cooling has become an increasingly effective method to prevent chemotherapy-induced hair loss. In particular, when anthracyclines or taxanes are used, good results have been shown but the dose should not be too high and the results were not so good if those cytostatics were combined. There is, however, a considerable variation in the success rates in the various studies and this remains unexplained. Unfortunately, many studies were small and badly designed and therefore difficult to compare.

If chemotherapy is given with a curative intent, scalp cooling should not be used in patients with extensive haematological malignancies as cooling might prevent the effect of chemotherapy on tumour cells in the scalp skin; in other patients, an adverse long-term effect of scalp cooling has not been described. The majority of patients tolerate cooling very well and side-effects are not frequent and not serious.

Further psychological, clinical and biophysical research is needed to determine the exact indications for cooling and to improve the hair-protective effect, tolerance, side-effects and the technical cooling procedure. Multicentre trials should be carried out to gather this information.

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