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Scalp Cooling has no Place in the Prevention of Alopecia in Adjuvant Chemotherapy for Breast Cancer

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35 patients were studied to determine the effectiveness of scalp hypothermia in the prevention of alopecia caused by adjuvant chemotherapy for breast cancer. Scalp hypothermia was induced by the newly developed Theracool™ cooling machine. The chemotherapeutic regimen consisted of one perioperative course of doxorubicin 50 mg/m², cyclophosphamide 600 mg/m² and 5-fluorouracil 600 mg/m² (EORTC protocol 10854). Only 4 (11%) patients showed acceptable hair preservation (no or minor alopecia). 12 patients (34%) had moderate alopecia, all requiring a wig. 19 patients (54%) had complete alopecia. No scalp metastases were observed after scalp cooling. These results and a review of the literature suggest that scalp hypothermia to prevent alopecia may only be effective in a cytotoxic regimen containing an anthracycline as the sole alopecia-inducing agent. With current adjuvant chemotherapy for breast cancer, in which a combination of cyclophosphamide and an anthracycline is often used, there is no place for scalp hypothermia.

Key words: alopecia, antineoplastic agents, hypothermia, induced, review
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INTRODUCTION

ALTHOUGH MOSTLY transient, alopecia is one of the most distressing side-effects of anti-cancer chemotherapy. This point was stressed by Kiebert and associates who showed that 88% of the women who received perioperative chemotherapy for breast cancer considered alopecia the most burdensome aspect of the treatment [1]. Some patients even refrain from cytotoxic treatment to avoid alopecia.

Scalp tourniquets and local hypothermia during the infusion of the cytostatic drugs have been used to reduce the incidence and severity of scalp hair loss. The rationale for both treatments is that it will temporarily reduce scalp skin circulation by constricting the superficial scalp vessels, thereby decreasing the amount of chemotherapeutics able to perfuse the hair follicles. The scalp hypothermia method has the additional theoretical advantage of reducing the temperature-dependent cellular uptake of drugs such as doxorubicin. In addition, scalp cooling may decrease the metabolic rate, making the hair follicles less susceptible to the toxic effect of chemotherapeutic drugs.

In general, the degree of alopecia is both drug and dose dependent. Among the drugs that are especially known to cause severe alopecia are doxorubicin, epirubicin and cyclophosphamide. Doxorubicin given as a single drug produces alopecia in

85-100% of patients, and an almost similar percentage of 75-90% alopecia is observed after intravenous cyclophosphamide [2]. Most of the cancer therapy regimens used today consist of a combination of drugs. We evaluated our own results with scalp hypothermia to prevent alopecia in a chemotherapeutic regimen with doxorubicin, cyclophosphamide and 5-fluorouracil given as a single course perioperatively. Additionally, the literature was reviewed to find out whether scalp cooling is reported to be effective, especially in a multi-drug combination with one of the drugs with a high risk for alopecia. Compact Cambridge Medline CD-ROM was used for searching the literature on scalp hypothermia and alopecia.

PATIENTS AND METHODS

Participating in the EORTC trial 10854, female patients under 70 years with operable breast cancer were randomised to receive CAF (cyclophosphamide, 600 mg/m²; doxorubicin, 50 mg/m²; 5-fluorouracil, 600 mg/m²) on the first postoperative day or no perioperative adjuvant chemotherapy. From January 1988 to December 1990, 35 patients receiving adjuvant chemotherapy for breast cancer at the Leiden University Hospital underwent scalp cooling, using the Novamedix Theracool System™ (Novamedix Ltd, Hampshire, U.K.). This newly developed scalp cooling device consists of a continuous flow system with a double layered cap connected to a thermostat-controlled cooling machine. The cap is placed tightly on the head of the patient after applying a generous amount of hair conditioner to the hair to increase the contact between scalp and cap. The cooling machine supplies a continuous flow of four cooling liquids

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through the cap. The scalp was cooled from 30 min before to 240 min after intravenous drug infusion. Scalp temperature was monitored in all patients. Shortly before anti-cancer drug infusion, 1 mg lorazepam, 10 mg methadonchloride and 20 mg metoclopramide were administered. Hair loss was evaluated using the World Health Organization (WHO) criteria for alopecia (grade 0: no hair loss; grade 1: minimal hair loss; grade 2: moderate hair loss, patchy alopecia; grade 3: complete hair loss, reversible; grade 4: complete hair loss, irreversible) [3]. Clinical and biochemical signs of liver metastases or impairment of the liver function (assessed from alkaline phosphatase and aspartate aminotransferase) were recorded at admission. Patients were seen at the outpatient department for follow-up at 3-month intervals during the first 2 years and at 6-month intervals thereafter.

RESULTS

35 patients received CAF adjuvant chemotherapy in combination with scalp cooling. The mean age was 50.3 years (range 28–69). There were no patients with clinical signs of liver metastases or abnormal alkaline phosphatase or aspartate aminotransferase. Scalp temperature stayed below 22°C during the whole post-infusion cooling time in all patients. The scalp cooling was tolerated well. Only 1 patient complained of a mild headache. In the third and fourth hour of cooling, the weight of the cap sometimes became uncomfortable. Premature termination of the scalp cooling was never necessary. Complications of the scalp cooling were not observed. 4 patients (11%) had WHO grade 0 or 1 (no or minor) alopecia. 12 patients (34%) had grade 2 (moderate) alopecia. All these 12 patients required a wig. 19 patients (54%) had WHO grade 3 (complete) alopecia. There were no patients with irreversible hair loss. In our earlier experience, during a phase 2 trial using the same therapeutic regimen, all patients ($n = 12$) developed complete alopecia during the course of this treatment. None of the patients that were treated with scalp hypothermia developed scalp metastases (mean follow-up time: 46 months).

DISCUSSION

Since the first article on hair conservation in cytostatic chemotherapy through scalp cooling was published in 1973 by Luce *et al.*, a considerable number of studies using this principle to prevent drug-induced alopecia have been reported (Table 1) [4]. Success rates found in the literature differ. Most series show acceptable hair preservation in 50–70% of the patients after hypothermia [1, 4–19].

We, as have some other groups, found a less successful effect of hypothermia [12, 13, 20]. Apart from the success rate, we will review other differences between the reported series.

Scalp cooling techniques

Several techniques were used to induce the hypothermia. With the exception of Luce and associates [4], who used chilled air for cooling, in the beginning most groups used simple bags with crushed ice, frozen cryogel packs, or packs with an endothermic cooling reaction for cooling the scalp. Later, special caps containing cryogel and an insulation layer were developed (Spenco Hypothermia CapTM, Howard-Stenner Cryogel CapTM, Kold KapTM, Hypotherm Gel Cap). The latest generation cooling caps are caps connected to a cooling device using air or fluid as a medium and equipped with a thermostat; such as ThermocirculatorTM, Fluid Circulator, TheracoolTM (this study), Cold Air Scalp Cooler. Although they provide more

controllable cooling that can be maintained for longer, there is no conclusive evidence that the permanently cooled caps give better hair preservation.

Working mechanism

The hair preserving effect of scalp cooling during cytostatic treatment can be partially explained by reduced blood flow leading to a minor dosage of drugs to the hair follicles. Bulow and colleagues demonstrated that blood flow is reduced to a constant level when the subcutaneous scalp temperature is below 30°C [21]. So a further decrease in scalp temperature does not result in a further reduction of scalp circulation. Gregory reported that the alopecia preventing effect was only obtained when the scalp temperature was reduced below 22°C and held reduced for at least 20 min [22]. These findings suggest that a reduction in local tissue metabolism, in response to low temperature rather than reduced blood flow, is the most significant factor in alopecia prevention by scalp cooling.

Cooling temperature

Limited data are available on the degree of cooling that must be obtained. Gregory described that hair conservation was only obtained when scalp temperature was reduced below 22°C [22]. Cooke and associates found that hair conservation only occurred when the scalp temperature was brought down to a level $\leq 24^\circ\text{C}$ [7].

Precooling time

Little has been reported regarding the time required to cool the scalp to a temperature $< 22\text{--}24^\circ\text{C}$ with each device as described above. Dean and colleagues, using a self-made turban with crushed ice for scalp cooling and a multi-channel electronic thermometry system for monitoring temperature, showed that scalp temperature fell from 37 to 32°C within 5 min of icing and to 26°C within five more min before stabilising at 23–24°C thereafter [23, 24]. Guy and colleagues, using the thermocirculator, also obtained scalp temperatures $\leq 25^\circ\text{C}$ within 15 min [20]. These data suggest a precooling time of at least 15 min. However, Dean practised a precooling time of only 5 min and this series showed a success rate of 70%. Accepting the 15-min criteria, only 14 of the 26 reviewed studies complied. The precooling time ranges from 5 to 20 min (30 min in this study).

Post-injection cooling time

In theory, scalp cooling needs to be utilised only during peak plasma drug levels. The first reports on scalp cooling as a hair-preserving technique, were studies with patients treated with a regimen containing doxorubicin as the sole alopecia-inducing drug. This drug, as do most of the other anthracyclines, shows plasma peak levels soon after a bolus injection that fall rapidly after an initial distribution phase with a half-life time of 1.9 h [25]. Thus, a 30-min period of scalp cooling after injection does effectively cover the period of highest plasma doxorubicin concentrations in normal patients.

Cyclophosphamide, another drug known to cause severe alopecia, has a different and more complex pharmacokinetic profile with a half-life in humans of 3.9–8.2 h and many active metabolites [26]. Wide interindividual variations in kinetic parameters of these metabolites have been found.

Most of the reviewed series use a cooling time of 30 min (range 15–60), probably taking the doxorubicin pharmacokinetics as their guideline.

Table 1. Overview of the reviewed articles

Source	R	C	Scalp cooling method	Cooling time (min)	Cytotoxic drugs and doses	Number of courses	Number of subjects	Scoring	% of patients with good hair preservation (control group)	Subgroups, % patients with good hair preservation (control group)
Luce <i>et al.</i> , 1973 [4]	-	+	Chilled air	5/10-10-20	D.n.s.	1	E = 12 C = 16	Max. % of hair loss	70% (20%)	
Edelstyn <i>et al.</i> , 1977 [5]	+	+	Cryogel bags	10/30	D50 V2 F500 (M5 + Ch 10) x 4	1	E = 40 C = 37	Graded scale	50% (19%)	
Dean <i>et al.</i> , 1979 [31]**	-	-H	Crushed ice	5/30	D30-40 intravenous C150 p.o. x 4	8	33	Subject photos Graded scale	70%	
Timothy <i>et al.</i> , 1980 [32]	-	-	Crushed ice	20/20	D90 or D50 + B + P + Vb	6	2	n.s.	100 (n = 2)	
Dean <i>et al.</i> , 1981 [24]**	-	-H	Kold Kap™	5/30	D30 C150 p.o. x 4 days	5 or more	25	Subject photos Graded scale	72%	
Dean <i>et al.</i> , 1983 [23]**	-	-H	Ice Packs (H) Kold Kap™	5-10/30-40	D30-40 C150 p.o. x 4	8	IP 35(16) KK 29(19) 32(28)	Subject photos Graded scale	IP 56% KK 63% 79%	
Anderson <i>et al.</i> , 1981 [6]**§	-	-	Cryogel packs 3M™	15/30	D40 + V2 or + Vd4 2 x per 28 days	2 or more	n.s.	n.s.	55%	
Cooke <i>et al.</i> , 1981 [7]**†	-	-	Cryogel packs 3M™	n.s.	D40 2 x per 28 days	n.s.	n.s.	n.s.	70% (38%)	D + C regimens 6% (4%)
Belpomme <i>et al.</i> , 1982 [11]	-	-H	Crushed ice bag	15/15	Multiple regimens e.g. D30-40 + C400-600	3	C = 77 E = 72(68)	No wig required	57%	D < 50pi 68% D + no C 64%
Goldhirsch <i>et al.</i> , 1982 [9]**†	-	-	Cryogel cap	10/30	Multiple regimens	2	82	No wig required < 50% hair loss	42% (5%)	D50pi 52% D + C 44%
Gregory <i>et al.</i> , 1982 [22]†	-	-H	Cryogel packs	20-30/30-40	D40 + V2 2 + per 28 days	3	24	Graded scale	66% (98%)	
Guy <i>et al.</i> , 1982 [20]	-	-H	Thermocirculator	15/30	D50 V1.3 C1000 M10	4	12	Graded scale Subject photos	79%	
Hunt <i>et al.</i> , 1982 [10]**§	-	-	Cryogel packs 3M™	15/30-4	(D40 + V2 or + Vd5) or D80	1-5	32(28)	Graded scale Subject photos	58%	D < 50pi 66% D > 50pi 52%
Kiser <i>et al.</i> , 1982 [8]**†	-	-	Cryogel pack	10/30	Multiple regimens	1-13	176	No wig required < 50% hair loss	78%	D + V 66% V 100%
Dixon-Hughes and Jones, 1984 [12]	-	-	Cap cooled by fluid circulator	n.s.	D + V or only V	n.s.	9 D + V 4 V	n.s.	70%	
Samonigg <i>et al.</i> , 1984 [13]	-	-	Ice cubes + pneumatic cap	10/50	D30-40 C200 p.o. 4 days	8	37	Graded scale		

Continued over

Table 1. Continued

Source	R	C	Scalp cooling method	Cooling time (min)	Cytotoxic drugs and doses	Number of courses	Number of subjects	Scoring	% of patients with good hair preservation (control group)	Subgroups †, ‡ % patients with good hair preservation (control group)
Satterwhite and Zimm 1984 [14]	+	+	Chemo Cap™	15/60	D20-60 + multiple combinations	C = 1.8 (1-5) E = 2.3 (1-10)	C = 13 E = 12	Graded scale	75% (8%)	D < 50pi 100% (33%) D > 50pi 57% (0%)
Whelock <i>et al.</i> , 1984 [28]	-	-	Kold Kap™	15/45	D50 C500 + C150 or + M20	1-5	11	Graded scale	0%	
Middleton <i>et al.</i> , 1985 [30]†	-	-	Cryogel packs or Spenco Cap	20/30	D40 V1.4 (C200 p.o. x 4)	3-6	60	Graded scale	0%	
Vendelbo Johansen, 1985 [15]	-	-	HypoTherm Gel-Kap™	15/30	D25 C400 F500 2 x per 28 days	2	65(61)	Graded scale	77%	ilf 29%
Symonds <i>et al.</i> , 1986 [16]	-	-	Cold air scalp cooling	15/30	multiple regimens D25-50	2	28(26)	Graded scale	77%	D50 C1000 V2 (n = 1) 0%
Villani <i>et al.</i> , 1986 [17]	-	+	Spenco Hypothermia Cap™	20/30	multiple regimens with D; dosage n.s.	2-6	C = 18 E = 18	Graded scale	2 courses—78% (50%) 6 courses—67% (17%)	
Robinson <i>et al.</i> , 1987 [18]	-	+	Howard-Stenner (cryogel) cap	20/45	D40-80	4 (mean)	E = 22 C = 10	Graded scale	72% (20%)	
David and Speechley, 1987 [19]	-	-	Cryogel packs	15/30-40	Multiple regimens dosage n.s.	n.s.	391(180)	Graded scale	Dtot 60%	D-ilf 14% D-nlf 79% D + C-42%
Giaccone <i>et al.</i> , 1988 [27]	+	+	Spenco Hypothermia Cap™	10/30	most patients: D50 C500	n.s.	C = 16 E = 19	Graded scale	37% (0%)	

* Reports from the same medical center; whether these reports are dealing with (partially) identical patient groups is not specified. † Southampton General Hospital; ‡ Insepsital Bern; § Royal Marsden Hospital, London; || Cancer Center University of Arizona & Tucson Veterans Administration Medical Center.
R, randomized; C, control group; + or - or H (historical controls), dose /, per m²; B, bleomycin; C, cyclophosphamide; Ch, chlorambucil; Ci, cisplatin; D, doxorubicin; M, Methotrexate; P, procarbazine; V, vincristine; Vb, vinblastine; Vd, vindesine; p.o., by mouth; E, experimental group; O, number of evaluable patients; IP, ice packs; KK, Kold Kap™; n.s., not specified; ilf, impaired liver function; nlf, normal liver function; pi, per injection; ††, Good hair preservation: no or only minor hair loss.

Chemotherapeutic regimens

Different chemotherapeutic regimens were used comprising a plethora of different drugs (doxorubicin, epirubicin, cyclophosphamide, 5-fluorouracil, vincristine, vinblastine, vindesine, methotrexate, bleomycin, DTIC, chlorambucil, cisplatin, dibromodulcitol, thiothepa, mitomycine C, dacarbazine, procarbazine) in several different dosages, e.g. doxorubicin 25–80 mg/m², cyclophosphamide 200–1000 mg/m².

Dose-related success: The degree of protection against hair loss is inversely proportional to the dose of the alopecia-inducing drug that is administered. This was demonstrated by treatment results from the Inselspital in Bern [8, 9]. Scalp hypothermia resulted in minor or no hair loss in 66% (49/74) of the patients when treated with doxorubicin \leq 50 mg per injection. When 50–70 mg doxorubicin per injection was used, only 52% (53/102) of the patients showed minor or no hair loss. When the doxorubicin dose was \geq 70 mg per injection, the success rate was reduced to 44% (26/59). A similar effect was seen by Satterwhite and Zimm 100% (5/5)—good hair conservation when a dose of \leq 50 mg doxorubicin per injection was used and 57% (4/7) when the dose was $>$ 50 mg [14].

Doxorubicin/cyclophosphamide combination: It is only in regimens with a low dosage combination of doxorubicin and cyclophosphamide that scalp cooling resulted in no or minor hair loss in a substantial number of patients. Dean and colleagues showed this, and reported minor or no hair loss in 70% of the patients using a regimen with doxorubicin 30 mg/m² + cyclophosphamide 150 mg oral \times 4 days [23].

In a higher dosage combination, such as those that are used in most adjuvant chemotherapy schemes for breast cancer, scalp cooling is less successful. Minor or no hair loss was reported in 6, 42, 37 and 0% of the patients, respectively, in four series reporting on high dose combinations [11, 19, 27, 28]. Only one report describes a higher success rate: 66% with no or only minor hair loss [20]. Even when the cooling time was prolonged to 240 min—considering the different pharmacokinetic profile of cyclophosphamide—the success rate was not improved as is demonstrated in our own series (11% minor or no hair loss).

Scalp metastases

Most authors caution that hypothermia should not be used in haematologic malignancies or other neoplastic diseases in which numerous stem cells might be present in the scalp. Indeed, one report describes scalp recurrence in a mycosis fungoides patient treated with scalp hypothermia [29]. 5 cases with scalp metastases after scalp hypothermia of 96 patients treated for disseminated breast cancer were also reported in two series [15, 30]. No case reports of scalp metastasis after scalp cooling for adjuvant chemotherapy for breast cancer were found in the literature.

CONCLUSION

Although much of the current information on scalp cooling is confusing, some points can be made. Cooling conditions have been optimised by development of cooling machines. Required cooling levels are known and easily met. A precooling time of at least 15 min is indicated. The post-injection cooling time required when using an anthracycline as a sole alopecia-inducing drug is at least 30 min. In these regimens, with an anthracycline as the sole alopecia-inducing drug, scalp cooling may be successful. However, when intravenous cyclophosphamide, another severe alopecia-inducing drug with a completely different pharmacokinetic profile, is combined with an anthracycline, even a

prolonged cooling time of 6 h does not suffice. Since most of the adjuvant therapeutic regimens for breast cancer nowadays contain a combination of cyclophosphamide and an anthracycline as doxorubicin or epirubicin, and taking into account the fact that success rates will even deteriorate when 4–12 cycles of chemotherapy are given, as in most of the actual treatment schemes, there is no use for scalp hypothermia to prevent alopecia in this setting.

Furthermore, the possibility that malignant cells are spared exposure to chemotherapy by use of scalp hypothermia limits its usefulness in especially metastatic disease.

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