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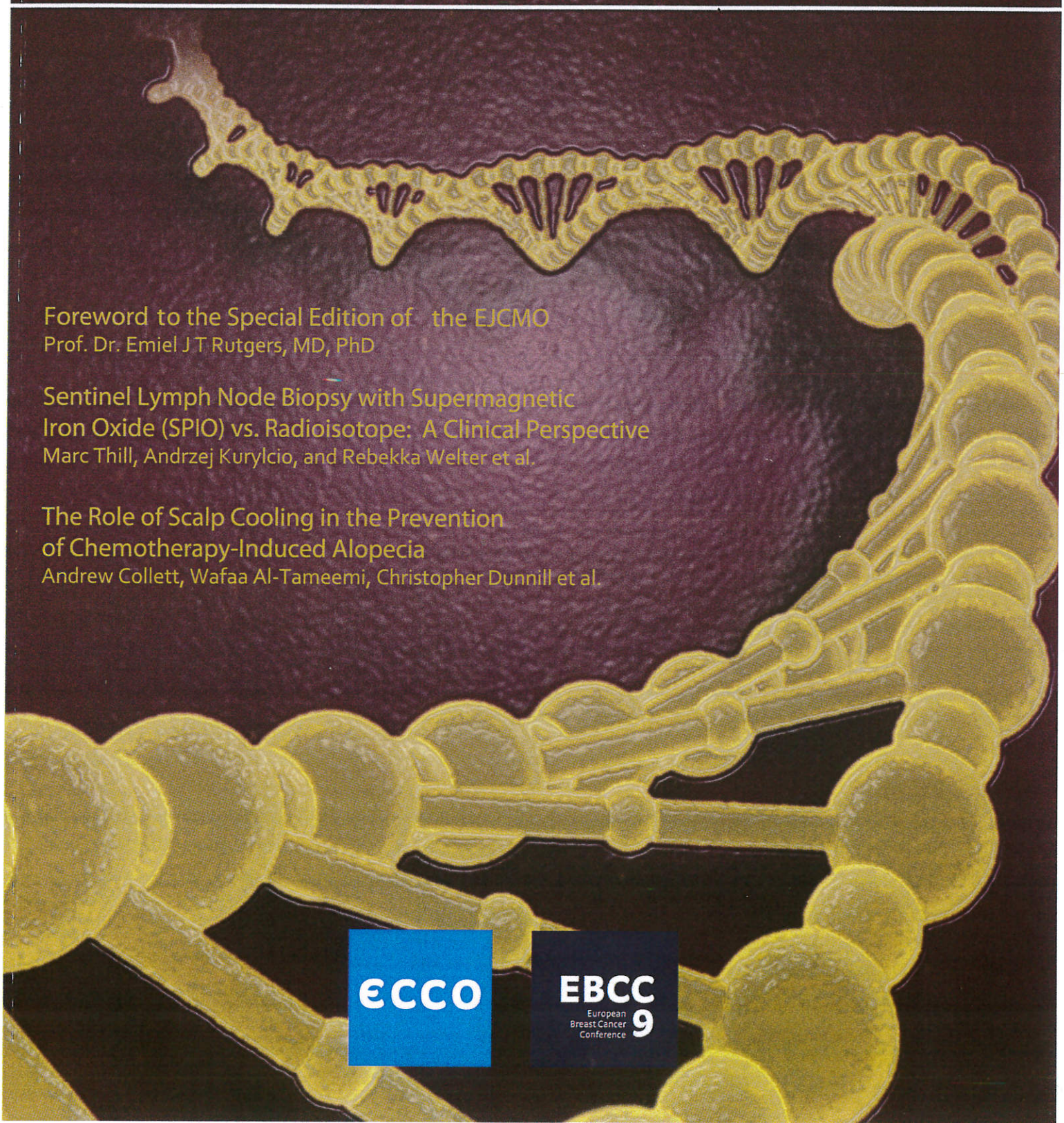

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The Role of Scalp Cooling in the Prevention of Chemotherapy Induced Alopecia

Authors: : *Andrew Collett[1], Wafaa Al-Tameemi[1], Christopher Dunnill[1], Omar Hussain[1,2], Nikolaos T. Georgopoulos[1]*

Affiliations: [1]*Department of Biology, School of Applied Sciences, University of Huddersfield, Huddersfield, U.K.;* [2]*Paxman Coolers Limited, International House, Fenay Bridge, Huddersfield, U.K.*

ABSTRACT

Chemotherapy induced alopecia (CIA) is widely regarded as the most traumatising side effect associated with cancer treatment and because of its association with cancer, deprives patients of privacy. The stress it causes can be detrimental to overall outcomes, however, there has been little research into its pathobiology and no pharmaceutical intervention is available. CIA is caused by chemotherapy damaging the rapidly dividing cells of the hair bulb it is normally reversible however, on regrowth the hair is often different in colour and/or texture and grows more slowly. The extent and incidence of CIA varies depending on the treatment regime on average it is 65% (range 0 - 100%). The only available treatment for CIA is scalp cooling, 2 techniques to achieve this are available; one uses pre-frozen cryogel caps the second uses a cap in which a refrigerated coolant is circulated, the advantage of this is that consistent cooling is maintained throughout drug infusion, the caps are more comfortable and are well tolerated. Scalp cooling probably works by a combination of vasoconstriction and a reduction in the metabolic rate of cells in the hair bulb. Its success varies from 0-90% depending on the chemotherapy agent and cooling technique. It is most successful for some mono-therapy, e.g. hair loss after docetaxel is reported to be reduced to 27% (without cooling it is about 80%). It is less successful for some combinatorial regimes such as TAC.

Keywords: Chemotherapy induced alopecia, Scalp cooling

INTRODUCTION

Hair loss is considered one of the most negative factors in cancer patient's care. The incidence of chemotherapy induced alopecia (CIA) is approximately 65% of all patients. [1] CIA compromises patient quality of life and can negatively impact on body image, sexuality and self-esteem, as well as depriving patients of their privacy, something that is often a particular burden for patients with younger children who have reported that this is the most traumatizing aspect of the treatment.[2] Collectively, these issues make CIA one of the most emotionally difficult side effects in terms of patients' experience it has been reported that some find losing their hair more difficult to accept than loss of their breast.[3] These factors are believed to lead to reduced therapeutic outcome, as stress and depression can weaken the immune system and this is linked to cancer progression.[4] Moreover, strikingly, it has been reported that up to 8% of female patients refuse chemotherapy for fear of hair loss.[5] Thus CIA should not just be considered as a cosmetic issue but one that can have a real effect on both patient outcome and quality of life. However, whilst considerable efforts have been expended in order to treat other side effects of chemotherapy and as a result, multiple drugs have been developed to control complications such as bone marrow suppression and toxicities, by contrast the pathobiology CIA is not well understood[6] and there are no drug-based treatments for CIA available.[7] The only treatment for CIA for which there is evidence of success is scalp cooling.

Pathobiology of CIA

The basic principle of chemotherapy is to damage the mitotic and metabolic processes in cancer cells.The reason this also affects hair follicles is that up to 90% of them will be in an active growth phase (anagen). During anagen, the hair follicle matrix cells (keratinocytes) are one of the fastest growing populations of cells in the body exceeding that of most malignant tumours[8] in addition the high blood flow rate around the hair bulb leads to the accumulation of the drugs. Chemotherapy induces keratinocyte apoptosis and hair follicle regression, as well as the impaired metabolic and mitotic processes in anagen hair follicles, all of which results in rapid and extensive alopecia.[7] CIA usually begins 2-4 weeks after chemotherapy and is complete with 1-2 months.[9] The varying degrees and severity of CIA depend on the types of chemotherapy drug, dose, route of administration and treatment schedule (Table 1).[7] A high intravenous dose usually causes more rapid and extensive hair loss. However, oral therapy at lower doses is likely to cause less alopecia even through the total dose may be higher.[10]

CIA is usually reversible, with re-growth starting 3-6 months after the end of the treatment, but permanent post-chemotherapy alopecia although rare has been reported.[9] However, even when hair regrows it is normally different in colour or shows greying and/or changes in hair structure and texture, such as becoming coarser. Furthermore, the rate of hair growth is significantly reduced.[1] Combination therapy consisting of two or more chemotherapy drugs produce a higher incidence of and more severe CIA compared to mono-therapy.[7]

Drugs that cause CIA

There are four major classes of anticancer drugs that commonly induce alopecia with an estimated incidence of >60% for alkylating agents (e.g., Cyclophosphamide), >80% for antimicrotubule agents (e.g., docetaxel), 60-100% for topoisomerase inhibitors (e.g., doxorubicin), and 10-50% for antimetabolites (e.g., 5-fluorouracil and leucovorin).[11]

More common or severe CIA		Less common or severe CIA	
Bleomycin	Cyclophosphamide	Amscarine	Busulfan
Cytarabine	Cisplatin	Carmusine	Chlorambucil
Dacarbazine	Dactinomycin	Carboplatin	Epirubicin
Docetaxel	Doxorubicin	Gemcitabine	Hydroxyurea
Etoposide	Fluorouracil	Interleukin-2	Melphalan
Idarubicin	Ifosfamide	Mercaptopurine	Methotrexate
Interferon-α	Irinotecan	Mitomycin C	Mitoxantrone
Mechlorethamine	Nitrosoureas	Procarbazine	Teniposide
Paclitaxel	Thiotepa	Vinorelbine	Busulfan
Topotecan	Vinblastine	Amscarine	Chlorambucil
Vincristine	Vindesine	Carmusine	

Table 1: Cytotoxic agents that can cause hair loss
Adapted from Luanpitpong and Rojanasakul (2012).[7]

Scalp Cooling

Scalp cooling or hypothermia during the administration of chemotherapy drugs has been shown to reduce hair loss[12] it has been used since the 1970s,[13] initially in only a few hospitals in the Netherlands. Recently, the numbers of countries and hospitals using scalp cooling has increased substantially. Two major commercially available products are used for scalp cooling. The first one is a refrigerated cryogel cap which is placed in a freezer at -25°C (e.g. Penguin cold cap); however, these gel-caps are reported to be uncomfortable and because they rapidly warm due to the heat generated by the head, they must be changed regularly (approximately every 20 mins) in order to maintain a constant scalp temperatureand thus several changes will be required during most standard chemotherapy perfusion protocols.[14] More recently, a significant advance in scalp cooling has occurred with the development of machines with a refrigeration unit which circulates a liquid refrigerant through a cap which come in a range of sizes so that a good fit can be obtained for a range of head sizes and shapes (e.g. Paxman Coolers PSC).[15] This technique has several significant advantages; it allows a constant scalp temperature to be maintained throughout drug infusion without the need for regular re-application of caps which saves time for medical staff. Also, because the caps are not cooled to such low temperatures and are not as heavy, they are more comfortable.

Scalp cooling is the only technique for which there is good evidence of efficacy in reducing CIA,[16] however, its mechanism of action is not fully understood although there are a few hypothesis as to how it could work. Firstly cooling causes blood vessel vasoconstriction, which has been shown to reduce blood flow in the scalp to 20-40% of the normal rate[17] and it has been suggested that this will result in less chemotherapeutic drug being delivered to the hair follicles.[18] Another possibility is that the rate of drug diffusion across a plasma membrane may be reduced by cooling and thus lower effective drug doses may enter the cells.[19] In addition, as cell division is metabolism-driven, it is possible that this process could be decelerated by cooling as temperature can particularly affect phases such as G1 and S,[20] which could be especially important for drugs that target specific phases of the cell cycle, such as microtubule-destructive drugs targeting mitosis. Also a decrease in the metabolic activity of the cells in the hair follicle could cause a more general reduction in the cytotoxicity of chemotherapy drugs.[18] In practice, it is likely that a combination of all of these methods have a role in the success of scalp cooling in reducing CIA.

In vitro experiments that have investigated the role of cooling in the reduction of the cytotoxicity of chemotherapy drugs on isolated rapidly dividing human keratinocytes, which represents a population of cells similar to the matrix keratinocytes of the hair root, which are damaged in chemotherapy, have provided evidence that cooling can protect these cells from toxicity caused by doxorubicin.[21] Our recent studies using similar in vitro cell models have shown that temperatures of 22°C or less provide almost complete rescue from the cytotoxicity of a range of chemotherapy drugs at concentrations similar to those expected to occur clinically (Al-Tameemi et al submitted for publication). Importantly, studies using the Paxman Coolers Orbis head cooling device have shown that 18°C can be consistently achieved in the scalp of patients throughout the course of chemotherapy infusion and have also reported that most patients tolerate this intervention very well, with the majority indicating either low or moderate levels of discomfort during cooling (Komen, personal communication).

A number of clinical studies have shown that the efficacy of scalp cooling can range from 0-90% depending on the chemotherapy agent and technique of cooling used.[13] However, undoubtedly it can be very effective for example, Auvinen et al (2010) showed that scalp cooling resulted in a significant reduction in CIA with 100% of patients maintaining their hair after doxorubicin treatment, 83.3% after docetaxel, 76.5% after FEC (fluorouracil, epirubicin and cyclophosphamide), and 78% after docetaxel in combination with FEC.[22]

Chemotherapy and planned dosage (mgr/m²)[a]	No head cover/total (%)	Number of sessions planned[d]
A60C600 (AC)	29/74 (39)	4
A60C600/D100[b] (ACD)	10/16 (63)	4/4
ACT Overall	20/50 (40)	
A60C600/T80[b] (ACT80)	14/29 (48)	4/12
A60C600/T175[b] (ACT175)	6/21 (29)	4/4
D75A50C500 (TAC)	5/66 (8)	6
D Over all[f]	87/120 (73)	
D75	31/33 (94)	n.a.
D100	27/44 (61)	n.a.
D75combi[c]	21/33 (64)	n.a.
F500A50C500 (FAC)	21/39 (54)	5
FEC Over all[f]	371/752 (56)	
F500E50 - 70C500 (FE50 - 70C)	22/38 (58)	5
F500/600E75 - 85C500/600 (FE75 - 85C)	16/32 (50)	5
F500E90C500 (FE90C)	292/558 (52)	5
F500/600E100C500/600 (FE100C)	40/123 (33)	6
F500E100C500/D100[b] (FE100CD)	22/46 (48)	3/3
TCarbo Overall[f]	31/68 (46)	
T70 - 100Carbo	9/12 (75)	n.a.
T175Carbo	20/52 (38)	6
T70 - 90	34/42 (81)	n.a.
Irino350	12/42 (29)	n.a.
Other[e]	49/64 (77)	
Total	**709/1411 (50)**	

A: doxorubicine; Carbo: carboplatin; C: cyclophosphamide; D: docetaxel; E: epirubicine; F: 5-fluorouracil; Irino: irinotecan T: paclitaxel. All 3-weekly schemes, with exception of /T80 and T70 - 90.

[a]Dosage other/missing, but included in multivariate analyses: TAC n = 1, FAC n = 4, FECD n = 6, T n = 2, Irino n = 5.
[b]Sequential scheme.
[c]Dcombi: D combined with Cyclophosphamide, Capecitabine, Carboplatin, Gemcitabine, Methotrexaat, Myocet or Xeloda.
[d]According to Dutch guidelines.
[e]Other: < 10 patients had a particular regimen with a specific dosage.
[f]Including also other dosages than specified in this table.

Table 2. Head cover use during the last scalp cooling session according to type of chemotherapy. Adapted from(23).

A larger prospective multi-centre study conducted by van den Hurk et al (2010) showed that besides the specific chemotherapy protocol, other factors may have an influence on the use of head cover for patients, such as age (generally it is lower in those over 50), female gender, ethnicity, hair length, quantity, waving, colouring, dyeing hair and wetting before scalp cooling.[23]

The duration of cooling can influence the protective effect of scalp cooling. Where possible the timing of cooling periods should be based on the pharmacokinetics of drugs.[24] However, with the use of combination therapies the plasma half-life of a number of drugs would need be taken into consideration. The optimal duration of scalp cooling so far has not been addressed but in most studies the precooling

time (i.e. the time between the start of scalp cooling and the administration of chemotherapy drugs) from 5 to 30 minutes has been used, this is to ensure that the scalp is cool when the drugs reach the hair follicles.[25-27] The cap remains in place during the administration of the drugs and also for a period after this (post infusion cooling time PICT) which allows the drug concentration to drop below toxic levels before the hair follicles warm up.

A study at the Medical Centre Alkmaar, measured scalp skin temperatures during cooling in both healthy volunteers and patients with cancer to determine the optimal pre-infusion cooling time using the Paxman scalp cooler, and in this study scalp temperature reached a constant level of approximately 18°C after 45 minutes (Komen, personal communication). Van den Hurk et al (2012) specifically examined the effect of post infusion scalp cooling time in reducing CIA after docetaxel treatment this showed that better results were obtained by reducing PICT from 90 min to 45 min (table 3).[28] This is presumably because once the bulk plasma concentration of docetaxel drops below toxic levels the warming of the scalp allows any drug that has accumulated during the course of chemotherapy to be more rapidly flushed out of the scalp. This study indicates that some optimisation of cooling protocols might be required to improve the efficacy for different chemotherapy regimens.

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

Table 3: Post infusion cooling times (PICTs)
Use of wig or head cover in scalp-cooled patients after treatment with docetaxel with different PICTs. *p00.04 (90 vs 45 min).
Adapted from (28).

In addition to the physiological and health benefits of hair retention during chemotherapy, a significant personal and societal financial saving by using scalp cooling has recently been demonstrated within the Dutch health care system.[29] This is because the cost of scalp cooling is significantly less than that required to purchase a wig.

Concerns have been raised that scalp cooling could be associated with a higher incidence of scalp metastasis however, no studies have provided any evidence for an increase in the risk of metastasis in the scalp which is a site where cancer recurrence is rare.[30] In fact the studies that have been conducted to specifically address this issue in patients with breast cancer firstly, confirm that scalp metastasis occur very rarely with an incidence between 0.03 and 3% in individuals that did not receive cooling and that this is no different to that for individuals who received scalp cooling 0.04 - 1%.[31]

Scalp cooling is a safe and well tolerated procedure which has been shown to significantly reduce the incidence of CIA which for many individuals is regarded as the most distressing side effect of cancer chemotherapy. The best results occur in conjunction with mono-therapy regimes although it also significantly reduces the incidence of CIA in number of other regimes including FEC. Further research is required to improve the efficacy of scalp cooling for more difficult to treat therapies such as TAC. There is good evidence that the best results are obtained when a scalp temperature of 22°C or less can be consistently maintained throughout the period of chemotherapy infusion and for a short time afterwards (post-chemotherapy infusion cooling) and these conditions are most consistently achieved by using a refrigerated scalp cooling device to which the cap is attached.

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Declaration

I declare that I have no competing interests.

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