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Prevention of chemotherapy-induced alopecia using an effective scalp cooling system

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Abstract

Alopecia is a distressing side-effect of cancer treatment. Taxanes (TX), anthracyclines (ANR) and etoposide (ET) have been consistently associated with significant alopecia. We studied an effective scalp cooling system, the Penguin Cold Cap system™, for the prevention of chemotherapy-induced alopecia in 70 patients receiving chemotherapy, including one of the following major alopecia-causing agents: Group A, TX-based regimes (without ANR); Group B, TX + ANR; Group C, ANR-based regimes (without TX); Group D, ET-based regimes. Protection from hair loss was achieved by maintaining scalp temperatures below 15°C before, during and after chemotherapy by frequent changing of the caps. Assessment was carried out using a grading system from 0 to 4. Grades 0–2 were considered as satisfactory hair protection, whilst Grades 3–4 were considered failures. 57 patients were evaluable for assessment. An overall 81% protection was achieved. In groups C and D 11 of 12 patients (92%) had no alopecia, whilst 30 of 34 patients (88%) treated with taxanes had adequate hair protection. In Group B, 4 of 11 patients (36%) had adequate hair protection. The system was well tolerated and is a very effective method for protection from hair loss caused by TX, ANR and ET. Our results are comparable with and, in most cases, better than those reported in other studies using various alopecia preventive methods.

Keywords: Alopecia; Taxanes; Anthracyclines; Etoposide; Scalp cooling

1. Introduction

Alopecia is one of the most unwelcome side-effects of chemotherapy. Although not life-threatening, it can be psychologically devastating and can even lead some patients to reject potentially curative treatment.

The degree of alopecia varies amongst different drugs. Chemotherapeutic agents such as the taxanes (TX), anthracyclines (ANR) and etoposide (ET) have been shown to have significant antitumour activity in solid tumours either alone or in combination regimes [1–6]. These drugs are also associated with significant alopecia as one of their main side-effects. The percentage of patients experiencing alopecia associated with the use of anthracyclines or taxanes is over 70% in most studies, whilst similar results have been reported for etoposide [7–11]. Alopecia induced by these agents is dose dependent, whilst its severity also depends on the combination of other cytotoxic agents [3,12].

A variety of different methods have been used for the prevention of chemotherapy-induced alopecia. These include scalp tourniquets, scalp cooling systems and immunomodulator techniques [13–16].

The cooling systems are based on the theory that by cooling the scalp, vasoconstriction is produced, which reduces the amount of drug delivered to the hair follicles. Cellular uptake by the hair follicle, which occurs more readily at warmer temperatures, is also reduced [17]. Several techniques have been used: bags with crushed ice, packs or caps containing cryogel and caps connected to a cooling device. Hair preservation is achieved in many cases, although studies showing failure of hair loss prevention have also been reported [18–20]. Recent studies have shown that the efficacy of a scalp cooling system is inversely associated with epi- and subcutaneous scalp temperatures [17,21]. Based on these findings, pre- and postchemotherapy scalp-cooling has been utilised in order to maintain steady, low scalp temperatures. Encouraging results have been reported in small studies, using anthracycline-containing regimes [17,18,22].

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The Penguin Cold Cap system™ is a scalp cooling system, which is based on previous research findings. The aim of this study was to evaluate the applicability and efficacy of this new cooling system in patients receiving various chemotherapeutic regimes that are frequently associated with significant alopecia.

2. Patients and methods

The Penguin Cold Cap system™ was studied in patients who received chemotherapy regimes containing at least one drug from three main alopecia-causing drug groups: taxanes (TX), anthracyclines (ANR) or etoposide (ET). No previous chemotherapy or brain radiotherapy was allowed. The method was approved by our Ethics Committee. The system was provided by MSC Hellas A.E.

The above cold cap system offers protection from hair loss by maintaining scalp temperatures below 15°C before, during and after chemotherapy by frequent changing of the caps. The caps are made of polyurethane material within which Crylon Gel, the cooling agent, is sandwiched. The caps were stored at −25°C and were transported to the patient in a container, thus avoiding significant warming. Velcro fasteners were used to permit easy and rapid close mounting of the caps to any sizes or shaped head with a fitting time of approximately 10 s.

The caps were applied by specially trained nurses who were provided by MSC Hellas A.E. The first cap was applied for 20 min. The second cap was applied for 35 min. All chemotherapeutic agents were administered intravenously. Paclitaxel was administered as a 3-h infusion, whilst docetaxel was infused within 1 h. Anthracyclines were administered as a bolus injection and etoposide was administered as a 2-h infusion. The chemotherapy infusion or injection was started in the first 10 min of the second cap. The caps were then changed every 35 min until the end of chemotherapy. Following the end of chemotherapy, caps were applied for 2 h, each cap being changed every 35 min. Extra caps were considered in individuals where hair thinning from previous treatments was noticed.

Alopecia was assessed by the attending physician at each visit using the following grading system, which is similar to that described by Dean and colleagues [23]: Grade 0: no hair loss; Grade 1: up to 25% hair loss; Grade 2: between 25 and 50% hair loss (without the need to wear a wig); Grade 3: between 50 and 75%; and Grade 4: greater than 75% hair loss. Alopecia of Grades 0–2 was considered adequate protection of hair loss, whilst alopecia of Grades 3 or 4 was considered as a failure of the system. Side-effects related to the application of the scalp cooling system were recorded at each chemotherapy visit by both the attending physician and the specialist nurse applying the caps.

Patients were considered evaluable if they had received at least two cycles of chemotherapy using the system. Patients who discontinued the system after 1 cycle of chemotherapy because of failure to offer adequate protection of hair loss (Grades 3–4 alopecia), were also evaluable.

Statistical analysis was performed using the χ^2 test with Yates correction.

3. Results

70 patients entered the study. Table 1 summarises patients' characteristics. The main tumour types treated were: lung cancer (20 pts, 30%), cancer of an unknown primary (11 pts, 16%) and breast cancer (9 pts, 13%). There was an even distribution of male and female patients with a mean age of 57 years (range: 25–75). The patients were divided into four groups according to the main alopecia-causing drug: Group A, TX-based regimes (without ANR); Group B, TX + ANR; Group C, ANR-based regimes (without TX); Group D, ET-based regimes (Table 2).

57 patients were evaluable for assessment, whilst 13 patients (19%) were non-evaluable: of these 8 patients (11%) stopped using the system after only one cycle of

Table 1
Patient characteristics

	n of patients (%)
Patients entered	70 (100)
Evaluable patients	57 (81)
Liver metastases	8
Elevated transaminases	1
Elevated transaminases, bilirubin	1
Non-evaluable patients	13 (19)
Stopped due to intolerability	8 (11)
Stopped due to disease progression	5 (7)
Male	35 (50)
Female	35 (50)
Mean age (years) (range)	57 (25–75)
Tumour type	
Lung	20
Cancer unknown primary	11
Breast	9
Endometrial	6
Ovary	4
Testis	4
Sarcoma	4
Non-Hodgkin's lymphoma	3
Renal	2
Stomach	2
Bladder	2
Melanoma	1
Pancreas	1
Nasopharynx	1

Table 2
Categorisation of patients according to the major alopecia-causing drug: Group A, taxanes; Group B, taxanes + anthracyclines; Group C, anthracyclines; Group D, etoposide

Group	Chemotherapy drugs	Doses (mg/m^2)	*n* of pts
A	Paclitaxel	175–250/3 weeks	6
	Paclitaxel/carboplatin	175–250/AUC 6/3 weeks	21
	Paclitaxel/gemcitabine	200/1000 $D_{1,8}$/3 weeks	4
	Paclitaxel/ifosfamide	175/1200 D_{1-3}/3 weeks	1
	Paclitaxel/ifosfamide/cisplatin	175/1500 D_{1-3}/70/4 weeks	1
	Docetaxel	50/week	2
	Docetaxel/gemcitabine	75/1000 $D_{1,8}$/3 weeks	2
	Docetaxel/ifosfamide	85/1200 D_{1-3}/3 weeks	1
	Docetaxel/vinorelbine	75/25 $D_{1,8}$/3 weeks	2
	Docetaxel/5-fluorouracil (5-FU)	75/500 D_{1-3}/3 weeks	2
	Total		42
B	Paclitaxel/epirubicin	175/80/3 weeks	8
	Paclitaxel/doxorubicin	150/60/3 weeks	3
	Paclitaxel/epirubicin/carboplatin	175/60/AUC[a] 5/3 weeks	3
	Total		14
C	Doxorubicin/cyclophosphamide	75/850/3 weeks	1
	Cyclophosphamide/epirubicin/vincristine	1000/75/1.5/3 weeks	3
	Methotrexate/vinblastine/doxorubicin/cisplatin	30 $D_{1,15,22}$/6 $D_{1,15,22}$/30/70/3 weeks	2
	Total		6
D	Etoposide/carboplatin	100 D_{1-3}/AUC 6/3 weeks	8
	Etoposide/bleomycin/cisplatin	20 D_{1-3}/15 D_{1-3}/40 D_{1-3}/3 weeks	2
	Etoposide/bleomycin/cisplatin/ifosfamide	180D_{1-5}/15D_{1-3}/20D_{1-5}/1200 D_{1-3}/3 weeks	1
	Total		8

[a] AUC, area under the concentration–time curve.

chemotherapy due to intolerability and the other 5 patients (7%) due to disease progression. 8 evaluable patients had liver metastases, 2 of which had abnormal liver function tests. The cumulative doses of the main alopecia-causing drugs administered to the evaluable patients are shown in Table 3.

Protection from hair loss achieved in the four groups studied is shown in Table 4. In Groups A, C and D, 25 of the 46 evaluable patients (54%) had no alopecia, 13 (28%) had Grade 1 alopecia, 4 (9%) had Grade 2 alopecia and only 4 patients (9%) had Grades 3 or 4 alopecia. Specifically, in Groups C and D only one patient experienced any Grade 2 alopecia. All patients in Group B experienced alopecia. One of the 11 evaluable patients (9%) had Grade 1 alopecia, 3 patients (27%) had Grade 2 alopecia and 7 patients (64%) had Grade 3 or 4 alopecia.

According to our definition of protection from hair loss, there was 88% protection in Group A, whilst the protection in Groups C and D was 100%. In Group B, where the regimes contained both taxanes and anthracyclines, there was only 36% protection. The protection

Table 3
Cumulative doses (mg/m^2) of the main alopecia-causing drugs administered to evaluable patients

Group	Drug	*n*	Mean ± 2 SEM[a]	Range
A	Paclitaxel	25	700 ± 131	175–1200
	Docetaxel	6	391 ± 93	200–500
	Paclitaxel + ifosfamide	2	350 ± 343 9450 ± 9700	175–525 4500–14 400
	Docetaxel + ifosfamide	1	340 14 400	
B	Paclitaxel + epirubicin	10	332 ± 122 145 ± 62	175–700 60–320
	Paclitaxel + doxorubicin	1	450 180	
C	Epirubicin	2	262 ± 73	225–300
	Doxorubicin	3	100 ± 53	60–150
D	Etoposide	6	990 ± 426	600–1800
	Etoposide + ifosfamide	1	1600 14 000	

[a] SEM, standard error of the mean.

Table 4
Degree of hair protection using the MSC cold cap system following chemotherapy with alopecia-inducing drugs: Group A, taxanes; Group B, taxanes + anthracyclines; Group C, anthracyclines; Group D, etoposide

Groups	Patients	Grade of alopecia *n* Patients (%)					Protection *n* patients (%)
		0	1	2	3	4	
A	34	14 (41)	13 (38)	3 (9)	2 (6)	2 (6)	30 (88)
B	11	0	1 (9)	3 (27)	4 (36)	3 (27)	4 (36)[a]
C	5	4 (80)	0	1 (20)	0	0	5 (100)
D	7	7 (100)	0	0	0	0	7 (100)
Total	57	25 (44)	14 (24.5)	7 (12)	6 (10.5)	5 (9)	46 (81)

[a] The difference in hair protection between Groups A and B is statistically significant ($P < 0.01$).

obtained by the cold cap system differed significantly between Groups B and A ($P < 0.01$). The overall protection for all treatment regimes was 81%. There was no correlation between hair protection and the presence of liver metastases or abnormal liver function tests.

Most patients complained of mild headaches, which were more noticeable in the longer regimes. Headaches occurred only during the application of the system and they rapidly resolved after the termination of scalp cooling. This was not a significant problem in most cases and only 8 patients (11%) discontinued the use of the system due to intolerability.

4. Discussion

Alopecia is a distressing side-effect of chemotherapy, having a negative impact on the quality of life of most patients [24]. Several methods of preventing chemotherapy-induced alopecia have been used over the years. The most widely applied method is the cooling of the scalp by a variety of techniques ranging from ice packs applied to the entire scalp to more sophisticated methods which use cryogel caps with or without tourniquets or cold air [13,20,23,25]. These methods are based on the rationale that scalp circulation is temporarily reduced, either mechanically or by vasoconstriction due to low temperatures achieved by the cooling, thus reducing the amount of the drug reaching the hair follicle. In addition, hypothermia can reduce the metabolic rate of the follicles, making them less susceptible to the effect of the chemotherapeutic agent.

The results of the abovementioned methods are generally promising but they also vary greatly. More detailed research has shown a close relationship between epi- and subcutaneous scalp temperatures [26] and that a subcutaneous temperature of 22°C has to be maintained for 20 min before significant protection can be obtained [17]. Therefore, the variation in the effectiveness of the methods reported in the literature might be, at least to a certain degree, due to a failure to achieve and maintain these temperatures for a sufficient length of time. The importance of pre- and post-chemotherapy cooling has been shown by a recent study, which concluded that a precooling time of at least 15 min as well as a postchemotherapy time of 30 min were required for best results [19].

We used a new, simple method, where caps, after being cooled, were carefully applied and fitted tightly over the scalp by specially trained staff, employed exclusively for the application of the system. It was well tolerated by the majority of patients. 8 patients could not tolerate the cold caps and discontinued the application of the system. They were all above 50 years of age and 5 of them were male. The ages of the 3 female patients were 57, 60 and 74 years, respectively. It can be postulated that in this group of 8 patients, appearance plays a less important role and, therefore, motivation to tolerate the mild side-effects of the system was possibly lacking.

The results reported in this study are promising with adequate protection achieved in 81% of the patients. This is in agreement with the best results published so far. To our knowledge, our study is one of the largest in the literature, including more than one group of major alopecia-causing cytotoxic agents. Patients receiving anthracyclines or etoposide had absolute protection. Although the number of patients in these groups was small, the Penguin system^{TM}, therefore, appears extremely effective, taking into consideration the high likelihood of significant alopecia in patients treated with these agents. The system is also effective in protecting from alopecia caused by taxanes. It offered protection in 88% of patients with 41% having absolute protection. We are aware of only one previous study, where a scalp cooling system was used to protect 98 patients receiving monotherapy with docetaxel from hair loss [16] with adequate protection reported in 86% of patients. It has to be stressed that our patients also received paclitaxel at the highest doses used in the literature (175–250 mg/m^2) with equally effective protection from hair loss and in most cases docetaxel was used in combination with other agents (Table 2). The results of the study of Lemenager and colleagues [16] as well as ours are important since the role of taxanes in the treatment of many frequent malignancies has become increasingly important. It appears that effective protection from hair loss can be offered and thus eliminate a significant drawback in the quality of life of patients treated with these agents.

The significant protection from hair loss, achieved with this system, may be due to a combination of improvements over older scalp cooling methods. It can achieve epicutaneous temperatures of 15°C, resulting in subcutaneous temperatures of 18°C, since the latter is approximately 3°C higher than the former [26]. This is lower than temperatures mentioned in the literature [17]. The system also provides more uniform scalp cooling than traditional ice packs, which are difficult to apply effectively. In our study, caps were carefully fitted tightly over the scalps by specially trained staff and extra Crylon Gel was provided in the occipital region and forehead thereby achieving an effective and uniform scalp temperature. In addition, each cap was applied for a maximum of 35 min, thus avoiding any loss of efficiency due to warming. Finally, up to 30 min of prechemotherapy and 2 h of postchemotherapy cooling was allowed, which are longer than those usually used [19]. In our study, similar application times were used for all groups. However, it is possible that results might be improved if these times were tailored to the

pharmacokinetics of each agent, i.e. using longer pre- and post-treatment cooling for taxanes which show longer half lives than anthracyclines and etoposide [27].

Another factor, which might also affect the result of the scalp cooling, is the slower catabolism of the chemotherapeutic agents due to liver function impairment. However, we found no relationship between hair protection and the presence of liver metastases. Furthermore, no correlation was found between hair protection and abnormal liver function tests. This is in agreement with the results reported by other investigators [16,28]. Nevertheless, it must be stressed that the number of such cases in our study was too small to draw definite conclusions. Another theoretical concern is the possibility of potentiating the occurrence of scalp metastases by the use of scalp cooling. Reassuringly, the number of cases reported so far is limited [16] and a relationship between scalp metastases and scalp cooling cannot, at present, be supported. Moreover, in our long experience using the Penguin system as well as other scalp cooling systems, we have observed no increase in the incidence of scalp metastases in our patients.

A potential disadvantage of the cold cap system used in this study is the amount of time required for the application of the system, adding approximately 2.5 h to the duration of each chemotherapy regime. Nevertheless, no additional hospitalisation is necessary and patients who participated in this study were willing to accept this prolongation of their hospital stay in exchange for the protection of hair loss achieved.

Our system provided protection of hair loss in 36% of patients treated with the combination of taxanes and anthracyclines. This is the first study reporting protection from alopecia caused by this particular combination. Our results are encouraging since all these patients would have experienced significant alopecia without protection [29]. Nevertheless, protection was significantly lower than that achieved when these agents were used separately. Therefore, an additive effect, resulting in a mechanism of hair destruction resistant to scalp cooling, can be postulated. The mechanism of this synergism is not clear but other types of anthracycline-induced toxicity are also enhanced by taxanes. Recent data showed that doxorubicin-induced cardiotoxicity is observed at lower than expected cumulative doses when used in combination with paclitaxel [30,31] and there is evidence that this additive toxicity is schedule dependent [32,33]. We, therefore, plan to study the effect of different schedules of anthracyclines combined with taxanes regarding the protection from hair loss achieved by the Penguin system™.

For the purpose of this study, the system was supplied by MSC Hellas A.E. However, an application to the Greek National Health System is already pending so that the system will in the near future be paid by the patients' National Health Insurance.

We conclude that the Penguin Cold Cap system™ is a very effective and well-tolerated method of protection from chemotherapy-induced alopecia. It offers protection to most patients treated with agents, which would, otherwise, cause significant hair loss. Further studies are required to clarify the mechanism of alopecia in the anthracycline–taxane combination and to develop methods of overcoming it.

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