Support Care Cancer (2002) 10:529–537
DOI 10.1007/s00520-002-0375-y

ORIGINAL ARTICLE

Christel Protière
Katrin Evans
Jacques Camerlo
Marie-Pierre d'Ingrado
Geneviève Macquart-Moulin
Patrice Viens
Dominique Maraninchi
Dominique Genre

Efficacy and tolerance of a scalp-cooling system for prevention of hair loss and the experience of breast cancer patients treated by adjuvant chemotherapy

Published online: 15 August 2002

C. Protière
INSERM U379,
232 boulevard de Sainte-Marguerite,
13273 Marseille Cedex 9, France

C. Protière
Research Group in Quantitative Economy
of Aix-Marseille II, Marseille, France

K. Evans · J. Camerlo · M.-P. d'Ingrado
G. Macquart-Moulin · P. Viens
D. Maraninchi · D. Genre (✉)
Medical Oncology Department,
Institut Paoli-Calmettes, 232,
Boulevard de Sainte-Marguerite,
13273 Marseille, Cedex 9, France
e-mail: oncomed@marseille.fnclcc.fr
Tel.: +33-4-91223537
Fax: +33-4-91223560

P. Viens · D. Maraninchi
University of Mediterranean
(Aix-Marseille II), Marseille, France

Abstract The applicability and efficacy of a scalp cooling system were studied in 105 breast cancer patients receiving four cycles of adjuvant chemotherapy with mitoxantrone + cyclophosphamide (NC chemotherapy). Women accepting the scalp-cooling system were compared for alopecia both against those who refused and against a "reference" group of 109 patients similarly treated but without being offered a scalp-cooling system. Hair loss in the 105 study patients was evaluated by nurses using World Health Organization (WHO) criteria at each cycle of chemotherapy. Concomitantly, tolerance and side-effects of the helmet were also recorded in 48 accepting patients. Similarly to reference group patients, a subsample of 27 accepting patients self-assessed hair loss using a specific questionnaire measuring its frequency and severity and the distress associated with this symptom. Nurses' ratings (n=105) indicated that hair loss frequency was constantly lower, at each cycle of chemotherapy, in study patients with scalp-cooling system (n=77) than in those without (n=28). Differences between the two groups were statistically significant at cycles 1 and 3 (P<0.05). When compared with those reported by reference group patients (n=109), study patients' self-measures of alopecia frequency (n=27) provided even more marked results than those achieved by nurses (cycles 1–3: P<0.01; cycle 4: P<0.05). Tolerance was generally good and no scalp metastasis was observed among the 77 accepting patients followed up. This study demonstrates that scalp cooling was an effective method of protection against hair loss caused by NC chemotherapy. Its routine use as part of adjuvant chemotherapy, especially in cancers with low prevalences of scalp metastasis, should be seriously considered.

Keywords Alopecia · Scalp-cooling system · Adjuvant chemotherapy · Hair preservation

Introduction

Among chemotherapy side-effects, nausea/vomiting and alopecia are the ones most feared by patients. The use of setrons has allowed vomiting to be enormously reduced, but the problem of alopecia still remains unresolved.

Nevertheless, hair loss is known to have a strong psychological influence on patients (alteration of self-image, self-esteem, feelings of difference in the eyes of others, evidence of the disease to the outside world, etc.) [3, 8, 24, 31]. Moreover, it induces different physical problems (discomfort caused by the capillary prosthesis, irritability because of hair loss, anxiety) [29]. Lastly, alopecia can incite some patients, particularly women, to totally refuse potentially curative treatment.

Consequently, alopecia is a cause of concern to clinicians involved in breast cancer care. In the context of standard breast cancer for which an adjuvant chemother-

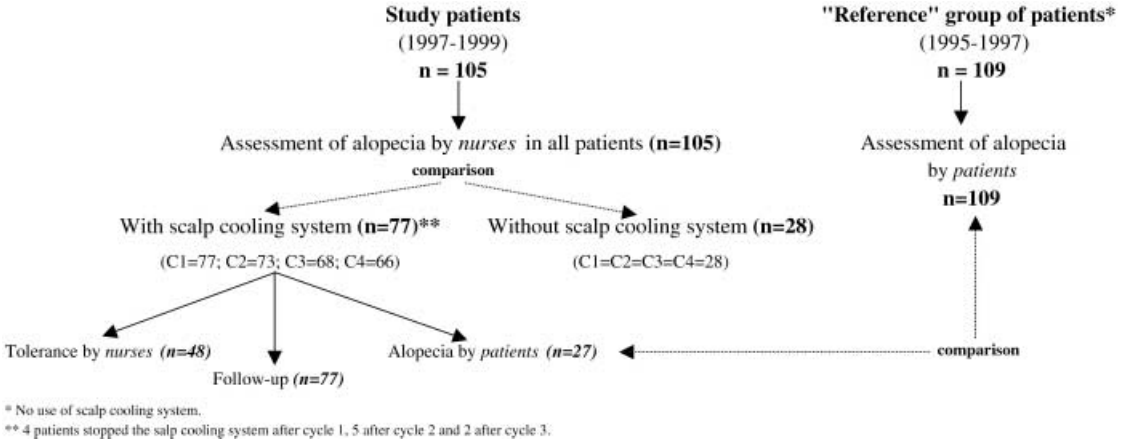

Fig. 1 Study design

apy is likely to be offered, the most commonly used regimen is a combination of cyclophosphamide, methotrexate and 5 fluorouracil (CMF) [5]. Another well-established active agent is doxorubicin, which is also widely used in combination with other agents [1, 6]. However, these drugs have severe toxic effects (hair loss, nausea and vomiting, mucositis, cardiomyopathy and marrow suppression). For this reason, several analogues and drugs with similar biochemical mechanisms have been developed with less toxic effects but similar efficacy. These drugs to which mitoxantrone belongs [4] are likely to be better accepted by patients.

This has led the clinicians to introduce mitoxantrone into adjuvant chemotherapy for standard breast cancer. Indeed, mitoxantrone is generally considered as well tolerated and associated with only moderate alopecia [14, 15, 20, 23, 25, 32]. Moreover, mitoxantrone has been reported to cause selective loss of white hair [2]. However, its toxicity, when associated with cyclophosphamide that is known as a severely alopecia-inducing drug, merited to be fully explored. A quality of life study carried out at the Institut Paoli-Calmettes (Marseilles, France) among 109 breast cancer patients receiving a regimen of mitoxantrone and cyclophosphamide (NC chemotherapy) in 4 cycles of 21 days showed that hair loss was reported by patients in about 74% of cycles [22], what remained relatively high. Following these findings, it was decided in the future to offer the use of a scalp cooling system to breast cancer patients included in the NC protocol.

The benefit of preventing hair loss, a problem due to antimitotics, was revealed about 30 years ago. It is based on the theory that reduction of cutaneous scalp circulation, produces vasoconstriction of blood vessels, and incidentally reduces the quantity of antimitotics which perfuse the capillary follicles. The first method described used compression with a tourniquet system. Then, only cooling methods were used, such as ice cubes, cryogels, propelled air and refrigerated helmets [9].

The aim of this paper is to report the applicability and efficacy of a scalp-cooling system (refrigerated helmet) in breast cancer patients receiving adjuvant chemotherapy associating mitoxantrone and cyclophosphamide. Women accepting the scalp cooling system were compared for alopecia to those who refused it and to patients included in the previous above-cited study.

Patients and methods

Study design is summarized in Fig. 1.

Patients

*Study patients (*n*=105)*

One hundred and five patients suffering from breast cancer with no metastases and fewer than nine involved axillary nodes received an adjuvant treatment associating polychemotherapy and concomitant or delayed radiotherapy. They were recruited at the Institut Paoli-Calmettes (Regional Hospital for Cancer Care) in Marseilles (France) between 10 February 1997 and 4 May 1999.

Chemotherapy doses were based on ideal body weight. The protocol (NC chemotherapy) comprised of mitoxantrone (12 mg/m^2) and cyclophosphamide (600 mg/m^2) administered in four cycles of 21 days in the outpatient clinic. Mitoxantrone (Novantrone) was administered as a 15-min i.v. infusion and cyclophosphamide (Endoxan) as a 30-min i.v. infusion on 1 day. Antiemetic prophylaxis consisted of granisetron (Kytril) administered in 1-mg tablet form 1 h before each cycle of chemotherapy and within 12 h after each first administration.

Patients were offered the scalp-cooling system by physicians after being informed of the technique of its use, its drawbacks, the potential risks (mainly scalp metastasis) and the anticipated effects [12]. Verbal, informed consent was required from all patients.

Scalp cooling was started with the first cycle of chemotherapy and given at each further cycle.

*"Reference" group of patients (*n*=109)*

These patients (*n*=109) were recruited at the Institut Paoli-Calmettes (Regional Hospital for Cancer Care) in Marseilles between 12 May 1995 and 4 February 1997, with the same inclusion

criteria as those required for study patients. The treatment protocol comprised the same polychemotherapy as that used in patients included in the current study and also radiotherapy administered concomitantly with chemotherapy. The scalp-cooling system was not proposed but these patients self-assessed their alopecia in the context of a prospective study of treatment side-effects [22].

Scalp-cooling system

The equipment used was the FRIGECAP helmet (PETERS LABO PHARMA), which required the hair to be moistened and the head protected with a cap. The helmet was worn for 15 min before and 45 min after treatment. Helmet temperature was checked after 45 min and the helmet was replaced if it had become warm (which happened in 4 of the 77 accepting patients). After use, it was removed, disinfected and decontaminated. After drying, the helmet was frozen (–25°C) for a minimum of 48 h.

Efficacy and tolerance of the scalp-cooling system

The efficacy and tolerance of the scalp-cooling system were assessed by nurses using a standard form developed by paramedical staff and a physician (D.G.). This form was completed by nurses consulting with the patients (face-to-face interview) at each cycle of chemotherapy. Hair loss was evaluated according to 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). Tolerance of the scalp-cooling system was assessed by the nurse applying and supervising its use. The patient was questioned during anticancer drug perfusion and the following 7 days. The 7-day assessment was retrospective and concerned the patient's experience during the previous cycle. Tolerance was rated as: very good, good, moderate, or poor. All side-effects related to helmet use reported by the patient were systematically noted by the nurse. To this end, she systematically questioned the patient on specific items (problems related to helmet weight and coldness, headache, neck pain), but also collected patient's spontaneous comments.

Patients' experience of hair loss

Hair loss was assessed by patients using a specific self-report questionnaire including three items measuring frequency, severity and distress associated with this symptom. This self-report questionnaire is a part of a 19-item self-report questionnaire used for measuring symptoms related to NC chemotherapy in the reference group of 109 patients [22]. Patients were asked about hair loss during the previous cycle. Severity of alopecia and the distress caused by it were scored on four-point scales ranging from 1 ("a little") to 4 ("totally") for severity and from 1 ("not at all") to 4 ("very much") for distress. The three-item self-report questionnaire was completed by patients at the start of each cycle of chemotherapy from cycle 2 onward, and at the visit made at the end of chemotherapy (planned for 1 month after the last cycle of chemotherapy). This administration schedule was the same as that used in the reference group of patients.

Statistical analysis

Statistical analysis was performed using SPSS software [28]. Qualitative data were analyzed using the Pearson Chi-square test (or Fisher exact test, if necessary). Quantitative data were compared by parametric (Student *t*-test) or nonparametric methods (Mann-Whitney test). At each cycle of chemotherapy, study patients accepting the scalp-cooling system (n=77) were compared for alopecia with patients who refused (n=28). In addition, a subsample of study patients (n=27) who accepted the scalp-cooling system and self-assessed their alopecia was compared with the reference group of 109 patients treated by NC chemotherapy who had similarly assessed their hair loss. Cohen's kappa coefficient [10] was used as the measure of agreement between the frequency of alopecia assessed by patients and that noted simultaneously by nurses (using WHO criteria). Based on general statistical guidelines [17], the strength of agreement was labeled as follows: ≤0.40, poor to fair agreement; 0.41–0.60, moderate agreement; 0.61–0.80, good agreement; 0.81–1, excellent agreement. Finally, tolerance of the scalp-cooling system was analyzed in a descriptive way. All statistical tests were two sided. Significance was assumed at 5%.

Results

Patients' characteristics

One hundred five patients were entered into the current study. Of 105 patients approached prior to cycle 1 of chemotherapy, 77 accepted the scalp-cooling system and 28 refused it. Among the 77 accepting patients, 4 definitively stopped using the system after cycle 1, 5 after cycle 2 and 2 after cycle 3 (Fig. 1).

Clinical characteristics of the study patients are presented in Table 1. There were no statistically significant differences in terms of age, hormonal status, number of involved axillary lymph nodes, type of surgery and modalities of administration of radiotherapy (before or after chemotherapy) between the patients who accepted the scalp-cooling system (n=77) and those who refused it during the entire course of radiotherapy (n=28). Furthermore, there were also no statistically significant differences for any of the initial characteristics between the 105 patients entered on the current study and the 109 patients included in our previous study (reference group patients). However, it must be noted that in the reference group radiotherapy was systematically administered concurrently with chemotherapy.

Efficacy of the scalp-cooling system as assessed by nurses: comparison of the patients with the scalp-cooling system (n=77) vs those without (n=28)

Table 2 shows the frequency of alopecia as assessed by nurses at each cycle of chemotherapy using WHO criteria, both in patients who accepted the scalp-cooling system and in patients who refused it. In Table 2, patients are classified as follows: no alopecia (WHO grade 0) and alopecia (WHO grades 1–4). After the first NC chemotherapy cycle, the frequency of alopecia was 13.0% among the patients who accepted the scalp-cooling system, as against 32.1% among those who refused it. Figure 2 shows the frequency of alopecia in the two groups after the first cycle of NC chemotherapy, this

Table 1 Patients' characteristics

	Study patients (*N*=105)		Reference group patients (*N*=109)
	Scalp cooling system (*n*=77)	No scalp cooling system (*n*=28)	No scalp cooling system (*n*=109)[b]
Characteristics[a]			
Age (years)	50 (25–73)	49 (29–72)	49 (29–73)
Hormonal status			
Nonmenopausal	34 (44.2%)	11 (39.3%)	59 (55.1%)
Menopausal	43 (55.8%)	17 (60.7%)	48 (44.9%)
Involved axillary lymph nodes	0 (0–8)	0 (0–12)	1 (0–25)
Surgery			
Tumorectomy	52 (67.5%)	18 (64.3%)	81 (78.6%)
Mastectomy	25 (32.5%)	10 (35.7%)	22 (21.4%)
Radiotherapy			
Concomitant with chemotherapy	52 (67.5%)	18 (64.3%)	109 (100%)
After chemotherapy	25 (32.5%)	10 (35.7%)	

[a] Number and percentage, except for age and number of involved lymph nodes (median and range)

[b] Incomplete numbers correspond to missing data

[c] Alone or after tumorectomy

Table 2 Alopecia assessed by nurses in the 105 study patients

	No scalp-cooling system (*n*=28)[a]	Scalp-cooling system (*n*=77)[a]
Cycle 1		
No alopecia	19/28 (67.9%)	67/77 (87.0%)
Alopecia	9/28 (32.1%)	10/77(13.0%)[b]
Cycle 2		
No alopecia	14/28 (50.0%)	46/73 (63.0%)
Alopecia	14/28 (50.0%)	27/73 (37.0%)
Cycle 3		
No alopecia	10/28 (35.7%)	40/68 (58.8%)
Alopecia	23/28 (64.3%)	28/68 (41.2%)
Cycle 4		
No alopecia	8/26 (30.8%)	29/66 (43.9%)
Alopecia	18/26 (69.2%)	37/66 (56.1%)

[a] Number (percentage); incomplete numbers correspond to missing data

[b] Comparison patients with vs without scalp cooling system: $P<0.05$

time broken down according to WHO alopecia grades. Not surprisingly, a progressive increase in frequency was observed in the two groups of patients over subsequent cycles. Differences between the two groups of patients were statistically significant for cycles 1 ($P=0.024$) and 3 ($P=0.038$). At the end of cycle 4, nurses noted hair loss in 56.1% of patients who accepted the system and in 69.2% in patients who refused it (NS).

Among the 105 study patients, nurses noted at least one episode of hair loss during the entire course of chemotherapy in 73.1% (76/104), while no episodes were noted in 26.9% (28/104). Compared with patients who were assessed by nurses as having had at least one episode of hair loss, patients without any episode of hair loss during the entire course of chemotherapy were more frequently assigned to receive concomitant radiotherapy [82.1% (23/28) vs 60.8% (45/74) – $P=0.041$]. When the data were examined cycle by cycle, it appeared that similar results were found for cycles 3 [76.9% (40/52) vs 57.1% (28/49) – $P=0.034$] and 4 [81.1% (30/37) vs 58.7% (37/63) – $P=0.022$], but not for cycles 1 and 2. Nevertheless, there was a similar percentage of patients who accepted use of the scalp cooling system in the two modalities of radiotherapy administration. Furthermore, there were no statistically significant relationships between alopecia and the four following variables: age, number of involved axillary lymph nodes, hormonal status, and type of surgery.

Efficacy of the scalp cooling system as assessed by patients: comparison of patients with scalp-cooling system (*n*=27) vs patients without (*n*=109)

Table 3 shows the frequency of alopecia self-assessed at each cycle of chemotherapy by a subgroup of 27 study patients who accepted the scalp-cooling system. Their assessments were compared with those provided by the 109 patients belonging to the reference group (no use of the scalp-cooling system). There were statistically significant differences between the two groups of patients for each cycle of chemotherapy ($P<0.01$ for the three first cycles and $P<0.05$ for the last cycle).

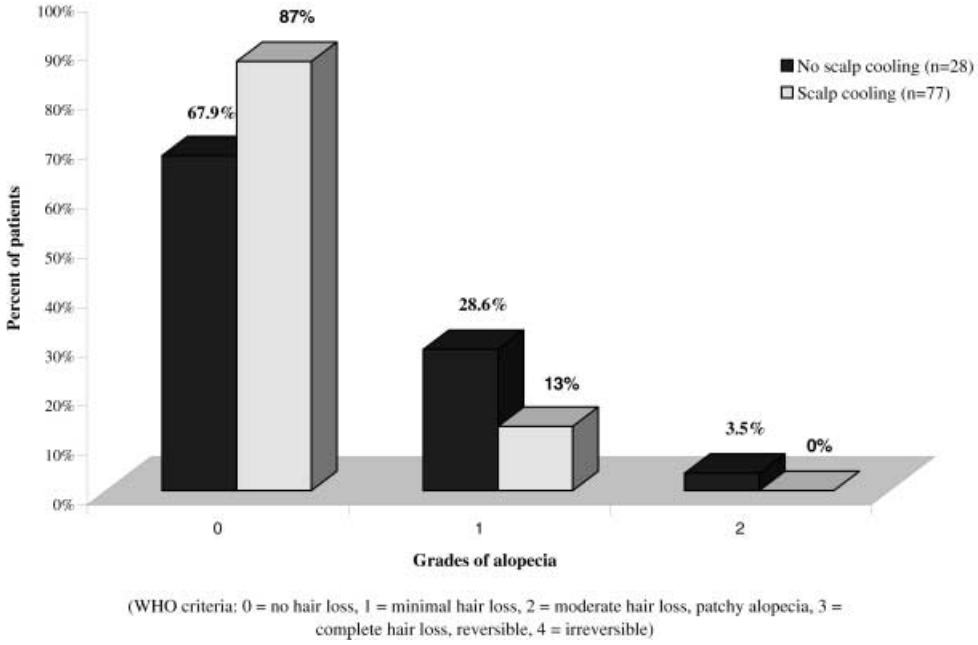

Fig. 2 Alopecia as assessed by nurses in the 105 study patients using WHO criteria (cycle 1)

Table 3 Frequency of alopecia assessed by a subsample of 27 study patients compared with the reference group of 109 patients

	No scalp-cooling system (Reference group – 109 patients)[a]	Scalp-cooling system (Current study – 27 patients)[a]
Cycle 1		
No alopecia	42/103 (40.8%)	19/27 (70.4%)
Alopecia	61/103 (59.2%)	8/27 (29.6%)’
Cycle 2		
No alopecia	24/102 (23.5%)	14/25 (56.0%)
Alopecia	78/102 (76.5%)	11/25 (44.0%)
Cycle 3		
No alopecia	19/101 (18.80%)	12/23 (52.2%)
Alopecia	82/101 (81.2%)	11/23 (47.8%)[c]
Cycle 4		
No alopecia	15/93 (16.1%)	9/22 (40.9%)
Alopecia	78/93 (83.9%)	13/22 (59.1%)[b]

[a] Number (percentage); incomplete numbers correspond to missing data
[b] Comparison of patients with vs without scalp-cooling system: $P<0.05$
[c] Comparison of patients with vs without scalp-cooling system: $P<0.01$

Alopecia frequencies self-reported by these 27 patients at each cycle of chemotherapy were compared with those noted simultaneously by nurses. According to Landis and Koch’s criteria, concordance between patients’ and nurses’ assessments was good for cycles 1, 2 and 3 (kappa coefficients = 0.72, 0.74, and 0.75, respectively) and excellent for cycle 4 (kappa coefficient = 0.91).

Table 4 displays alopecia severity and distress scores (range: 1–4), reported both by the 27 study patients agreeing to use the scalp cooling system and the 109 reference group patients (no use of the scalp-cooling system). Table 4 shows that the percentage of patients giving severity and distress scores 3–4 (high intensity of severity/distress) was lower, at each cycle of chemotherapy, in patients with scalp cooling system than in patients without. However, differences between the two groups of patients were not statistically significant both for severity and distress scores in none of four cycles of NC chemotherapy ($P>0.05$).

Tolerance and safety of the scalp cooling system (n=48)

Tolerance of the scalp cooling system was evaluated in 48 patients of 77 accepting patients. Table 5 displays tolerance scores at each cycle of chemotherapy before and after perfusion and shows high tolerance scores both during and after perfusion.

Table 4 Severity and distress caused by alopecia, assessed by a subsample of 27 study patients compared with reference group of 109 patients

	No scalp-cooling system (Reference group – 109 patients)[a]	Scalp-cooling system (Current study – 27 patient)[a]
Cycle 1		
Severity scores 1–2	51/61 (83.6%)	7/8 (87.5%)
Severity scores 3–4	10/61 (16.4%)	1/8 (12.5%)
Distress scores 1–2	27/48 (56.2%)	6/8 (75.0%)
Distress scores 3–4	21/48 (43.8%)	2/8 (25.0%)
Cycle 2		
Severity scores 1–2	58/78 (74.4%)	11/11 (100.0%)
Severity scores 3–4	20/78 (25.6%)	0/11 (0.0%)
Distress scores 1–2	30/71 (42.3%)	11/11 (100.0%)
Distress scores 3–4	41/71 (57.7%)	0/11 (0.0%)
Cycle 3		
Severity scores 1–2	62/82 (75.6%)	11/11 (100.0%)
Severity scores 3–4	20/82 (24.4%)	0/11 (0.0%)
Distress scores 1–2	30/69 (43.5%)	6/11 (54.5%)
Distress scores 3–4	39/69 (56.5%)	5/11 (45.5%)
Cycle 4		
Severity scores 1–2	52/78 (66.7%)	12/13 (92.3%)
Severity scores 3–4	26/78 (33.3%)	1/13 (7.7%)
Distress scores 1–2	31/72 (43.1%)	8/13 (61.5%)
Distress scores 3–4	41/72 (56.9%)	5/13 (38.5%)

[a] Number (percentage). Severity score ranges from 1 (“a little”) to 4 (“totally”) and distress score from 1 (“not at all”) to 4 (“very much”).These scores were calculated when symptom was present. Incomplete numbers on distress scores correspond to missing data. Comparison of study patients vs reference group patients: $P>0.05$ for all statistical differences

Table 5 Evaluation of tolerance of the scalp-cooling system, during and after perfusion, in a subsample of 48 study patients

	During perfusion[a]		After perfusion[a]	
	Very good/good	Moderate/poor	Very good/good	Moderate/poor
Cycle 1	35/48 (75.0%)	12/48 (25.0%)	42/48 (87.5%)	6/48 (12.5%)
Cycle 2	33/44 (75.0%)	11/44 (25.0%)	35/44 (79.5%)	9/44 (20.5%)
Cycle 3	32/41 (78.1%)	9/41 (21.9%)	30/41 (73.2%)	11/41 (26.8%)
Cycle 4	28/39 (71.18%)	11/39 (28.2%)	31/39 (79.5%)	8/39 (20.5%)

[a] Number (percentage); incomplete numbers correspond to patients who stopped using the scalp-cooling system (4 after cycle 1, 3 after cycle 2 and 2 after cycle 3) and/or to missing data

In this sample of 48 patients, 4 patients stopped using the scalp-cooling system after the first cycle of chemotherapy because of neck pain, fear of skin metastasis, sinusitis, or febrile syndrome; 3 withdrew after the second cycle because of headaches or cold sensations or for personal reasons; and 2 patients after the third cycle because of psychological rejection and intolerance to wearing the helmet. During chemotherapy perfusion, patients’ comments essentially concerned the weight of the helmet, pronounced coldness for 5–10 min or a feeling of burning and headaches. After perfusion, the following symptoms were the most frequently described : headaches, neck pain, and psychological difficulties in wearing the helmet (violent aversion to cold, ice and freezing).

Patient follow-up (n=77)

After a median follow-up of 44 months (range: 23–63) from the start of chemotherapy, none of patients who had accepted the scalp-cooling system (n=77) had reported manifested scalp metastasis.

Discussion

The aim of this study was to test the efficacy of a scalp-cooling system in the prevention of hair loss in women suffering from breast cancer treated by a chemotherapy regimen associating mitoxantrone and cyclophosphamide (NC chemotherapy) and to explore patients’ experience.

Among the methods of alopecia prevention, the hypothermic methods, used since 1978, have become the most widely used [9, 12]. Two studies have shown that the efficacy of the hypothermic methods is inversely associated with epi- and subcutaneous scalp temperatures [7, 13, 18]. Based on these studies, a pre- and postchemotherapy scalp-cooling system has been used to maintain steady, low scalp temperatures. The temperature lev-

el obtained at scalp level is also a cause of concern for investigators. Gregory [13] reported that hair preservation was only obtained when scalp temperature was reduced below 22°C, while for Cooke et al. [11] hair conservation only occurred when the scalp temperature was reduced to 24°C or below. Another subject of discussion is the duration of scalp cooling required both before and after chemotherapy infusion. According to Tollonear et al. [30], cooling times of at least 15 min before and at least 30 min after the infusion are indicated when anthracycline is used as the sole alopecia-inducing drug. In the recent study published by Katsimbri et al. [16], the period of application of their scalp-cooling system added approximately 2.5 h to the duration of each chemotherapy session. When refrigerated at –25°C for 24 h, the scalp-cooling system used in our study might maintain a temperature below 25°C for 60 min. Pre- and postinfusion cooling times of 15 min and 45 min, respectively, were in accordance with those advocated by Tollonear et al. [30]. Furthermore, it must be noted that in our study, the helmet was replaced because of warming only in 5% of patients, which is very low. Some of mitoxantrone's pharmacokinetic characteristics may explain the relative efficiency of the scalp-cooling system. Indeed, in previous pharmacokinetic studies, the initial drug distribution phases were shown to be very short, with T 1/2α and T 1/2β of 2.5 and 16 min. [20]. Consequently, in our study, the cooling duration exceeded the length of exposure to high plasmatic mitoxantrone concentrations, potentially contributing to the reduction in hair toxicity.

Reaching a consensus on the effectiveness of scalp cooling has been hampered by the large variety of cytotoxic agents and doses used, the small patient cohorts and a failure to randomize patients or to incorporate comparative groups [16, 19, 26, 27, 29, 30]. Another limitation was the use of nonstandard methods or criteria of hair loss evaluation (mainly, photos of patient scalp, graded scale, use or not of a wig). Furthermore, they also failed to take direct account of the patients' point of view in parallel with physicians' or nurses' measures.

Our study has the advantage of comparing the study patients accepting the scalp-cooling system with those refusing it and also with a reference group of 109 women previously treated with the same chemotherapy protocol but without the use of a scalp-cooling system. The number of patients entered was relatively large (n=105), and alopecia was assessed by nurses for all patients and also by the women themselves in a subsample of 27 patients.

However, some limitations of this study merit discussion. First, patients were not randomized. Indeed, we deliberately decided against the randomization procedure, for ethical considerations. Furthermore, we knew that patients were aware of the possibility of using the scalp-cooling system and were entirely free to request the procedure from the medical team. In addition to this, we already had access to a large group of patients treated by NC chemotherapy who were not offered the scalp-cooling system. Statistical analysis demonstrated that patients included in the current study presented similar initial clinical characteristics to those belonging to the reference group. Second, tolerance of the helmet was studied in only 48 of 77 accepting patients, and the self-measures of alopecia were performed on a small subsample (n=27) of these same patients. The reasons for this were only logistical. In particular, it was not easy to submit the study patients to a double evaluation of their hair loss in the context of the outpatient clinic. It is possible also that uneven numbers in different groups of patients could induce bias in the results of comparative analyses. Finally, the study would have had to be completed by an evaluation of the costs of the procedure in terms of time invested by nurses and the time a patient occupied a place in the outpatient clinic. This evaluation would show whether or not a method which can provide a global decrease in alopecia frequency by about 22–31% (depending on whether the alopecia assessment was done by nurses or patients) can be justified. The burden for the patient should also be considered. However, it must be noted that in our study the majority of women were very satisfied with the procedure. Despite some criticisms, we believe that data obtained in this study are useful and have important implications for patients' well-being.

This study clearly demonstrates the efficacy of the scalp-cooling system in preventing alopecia induced by NC chemotherapy. At cycle 4, nurses noted hair loss in 56.1% of those accepting the system vs 69.2% in patients who had refused it (NS). For the subsample of 27 patients who self-assessed their alopecia and who were compared with the reference group of 109 patients without the scalp-cooling system, results were even more marked. (At cycle 4, hair loss was reported in 59.1% of patients who used the scalp-cooling system, as against 83.9% of patients who did not (P=0.017). In contrast to our previous experience with physicians [21], concordance between patients' and nurses' reports was high.

Our results can be favorably compared with those of Ron et al. [27], who found 47% hair loss in patients with scalp-cooling system vs 81% without (P=0.014). Their study group of 35 breast cancer patients consisted of 19 hypothermically treated patients and 16 age-matched control patients treated at ambient temperature. All were treated with the same highly depilatory protocol CMF (cyclophosphamide, methotrexate and 5-fluorouracil). Our findings concerning a higher frequency of hair loss at cycles 3 and 4 in patients assigned to sequential treatment may be explained as the expression of some apprehension at the prospect of a second complementary therapy, i.e. the radiotherapy. This situation would not arise in patients receiving concurrent radiochemotherapy who had reached the end of treatment.

Compared to the "reference" group of 109 patients, the severity and distress associated with hair loss were

always lower at each chemotherapy cycle in the subsample of 27 patients who self-assessed their hair loss and who used the scalp cooling system. These results confirm the effectiveness of the scalp cooling system and demonstrates the additional benefit in stress reduction.

Although there were 4 cases of withdrawal from scalp-cooling in the subsample of 48 patients evaluated with regard to scalp-cooling system tolerance, patients' acceptability was high. Complaints were in keeping with those reported by other investigators. In spite of problems encountered, women were generally very satisfied with their choice and did not regret their decision to accept the scalp-cooling system. In fact, the majority considered that the psychological comfort related to its use outweighed minor physical difficulties.

Despite the doubts about the efficacy of scalp hypothermia for some drugs and questions remaining about subsequent scalp metastases, scalp hypothermia appears simple, relatively easy for nursing staff, low cost and low-risk. As patients' quality of life becomes a priority, the routine use of a scalp-cooling system as part of adjuvant chemotherapy, especially in cancers with a low prevalence of scalp metastasis, should be seriously considered. This technique can help maintain patients' self-image and thereby reduce the devastating psychological effects associated with cancer, and, sometimes, still more with its treatment.

Acknowledgements We wish express our gratitude to PETERS LABO PHARMA for providing the FRIGECAP helmet used in this study. We also thank the patients and the members of the Medical Oncology Department of the Institut Paoli-Calmettes for their contributions to this work.

References

1. Aisner J, Weinberg V, Perloff M, et al (1987) Chemotherapy versus chemoimmunotherapy (CAF v CAFVP v CMF Each +/- MER for metastatic carcinoma of the breast. A CALGB study. J Clin Oncol 5:1523–1533
2. Arlin ZA, Friedland ML, Atamer MA (1984) Selective alopecia with mitoxantrone. N Engl J Med 310:1464
3. Batchelor D. (2001) Hair and cancer chemotherapy: consequences and nursing care – a literature study. Eur J Cancer Care 10:147–163
4. Bennett JM, Muss HB, Doroshow JH, et al (1988) A randomized multicenter trial comparing mitoxantrone, cyclophophamide, and fluorouracil in the therapy of metastatic breast carcinoma. J Clin Oncol 6:1611–1620
5. Bonadonna G, Valagussa P, Moliterni A et al (1995) Adjuvant cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer. The results of 20 years of follow-up. N Engl J Med 332:901–906
6. Bull JM, Torney DC, Li SH, et al (1978) A randomized comparative trial of Adriamycin *versus* methotrexate in combination drug therapy. Cancer 41:1649–1657
7. Bulow J, Friberg L, Gaardsting O, Hansen M (1985) Frontal subcutaneous blood flow, and epi- and subcutaneous temperatures during scalp cooling in normal man. Scand J Clin Lab Invest 45:505–508
8. Carpenter JS and Brockopp DY (1994) Evaluation of self-esteem of women with cancer receiving chemotherapy. Oncol Nurs Forum 21:751–757
9. Cline BW (1984) Prevention of chemotherapy-induced alopecia: a review of the literature. Cancer Nurs 7:221–228
10. Cohen J (1968) Weighted kappa: nominal scale agreement with provision for scaled disagreement or partial credit. Psychol Bull 70:213–220
11. Cooke T, Gregory RP, Middleton J, Williams C (1981) Prevention of doxorubicin-induced alopecia. BMJ 282:734–735
12. Dorr VJ (1998) A practitioner's guide to cancer-related alopecia. Semin Oncol 25:562–570
13. Gregory RP, Cooke T, Middleton J, Buchanan RB, Williams CJ (1982) Prevention of doxorubicin-induced alopecia by scalp hypothermia: relation to degree of cooling. BMJ 284:1674
14. Hainsworth JD, Andrews MB, Johnson DH, Greco FA (1991) Mitoxantrone, fluorouracil, and high-dose leucovorin: an effective, well-tolerated regimen for metastatic breast cancer. J Clin Oncol 9:1731–1735
15. Hirvikoski PP, Kumpulainen EJ, Johansson RT (1997) CNF combination as adjuvant treatment in breast cancer patients is well tolerated. Anticancer Drugs 8:376–378
16. Katsimbri P, Bamias A, Pavlidis N (2000) Prevention of chemotherapy-induced alopecia using an effective scalp cooling system. Eur J Cancer 36:766–771
17. Landis RJ, Koch GG (1977) The measurement of observer agreement for categorical data. Biometrics 33:159–174
18. Lemenager M, Genouville C, Bessa EH, Bonneterre J (1995) Docetaxel-induced alopecia can be prevented. Lancet 346:371–372
19. Lemenager M, Lecomte S, Bonneterre ME, et al (1997) Effectiveness of cold cap in the prevention of docetaxel-induced alopecia. Eur J Cancer 33:297–300
20. Lenk H, Muller U, Tanneberger S (1987) Mitoxantrone: mechanism of action, antitumor activity, pharmacokinetics, efficacy in the treatment of solid tumors and lymphomas, and toxicity. Anticancer Res 7:1257–1264
21. Macquart-Moulin G, Viens P, Genre D, et al (1997) Discordance between physicians' estimations and breast cancer patients' self assessments of side-effects of chemotherapy: An issue for quality of care. Br J Cancer 76:1640–1645
22. Macquart-Moulin G, Viens P, Genre D, et al (1999) Concomitant chemoradiotherapy for nonmetastatic breast carcinoma: side-effects, quality of life, and daily organization. Cancer 85:2190–2199
23. Panasci L, Shenouda G, Begin L, et al (1990) Mitomycin C and mitoxantrone chemotherapy for advanced breast cancer: efficacy with minimal gastrointestinal toxicity and alopecia. Cancer Chemother Pharmacol 26:457–460
24. Pickard-Holley S (1995) The symptom experience of alopecia. Semin Oncol Nurs 11:235–238
25. Posner LE, Dukart G, Goldberg J, Bernstein T, Cartwright K (1985) Mitoxantrone: an overview of safety and toxicity. Invest New Drugs 3:123–132
26. Robinson MH, Jones AC, Durrant KD (1987) Effectiveness of scalp cooling in reducing alopecia caused by epirubicin treatment of advanced breast cancer. Cancer Treat Rep 71:913–914

27. Ron I, Kalmus Y, Kalmus Z, Inbar M, Chaitchik S (1997) Scalp cooling in the prevention of alopecia in patients receiving depilating chemotherapy. Support Care Cancer 5:136–138
28. SPSS (1993) SPSS-X Users' guide (release 6.0).
29. Tierney AJ (1987) Preventing chemotherapy-induced alopecia in cancer patients: is scalp cooling worthwhile? J Adv Nurs 12:303–310
30. Tollenear RAEM, Liefers GJ, Repelaer van Driel OJ, van de Helde CJH (1994) Prevention of chemotherapy-induced alopecia using an effective scalp cooling system. Eur J Cancer [A] 30:1448–1453
31. Williams J, Wood C, Cunningham-Warburton P (1999) A narrative study of chemotherapy-induced alopecia. Oncol Nurs Forum 26:1463–1468
32. Wils JA (1993) Mitoxantrone, leucovorin and high-dose infusional 5-fluorouracil: an effective and well-tolerated regimen for the treatment of advanced breast cancer. Eur J Cancer [A]29:2106–2108