PREVENTION OF CHEMOTHERAPY-INDUCED HAIR LOSS BY SCALP COOLING

E. G. Grevelman1 and W. P. M. Breed2*
University of Maastricht, Nassaulaan 11a, 6224 JT Maastricht; 2Department of Internal Medicine, Catharina Hospital, Eindhoven, The Netherlands Received 22 June 2004; accepted 26 October 2004

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

Methods: This review from 53 publications and three personal communications focuses on the efficacy of the treatment, side-effects, possible disadvantages and the controversies in these areas.
Results: Scalp cooling has become an increasingly effective method to prevent hair loss, especially when anthracyclines or taxanes are used. Unfortunately, many studies were small and badly designed and are therefore difficult to compare. There is a considerable variation in the success rates in the various studies. This remains unexplained, but the cooling time, the chemotherapy used and the temperature seem to be influential. Scalp cooling should not be used if chemotherapy is given with a curative intent in patients with generalized haematogenic metastases. The majority of patients tolerate cooling very well.

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

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

Effectiveness of Cold Cap in the Prevention of Docetaxel-induced Alopecia

M. Lemenager,[1] S. Lecomte,[1] M.E. Bonneterre,[1] E. Bessa, [2] J. Dauba [1] and J. Bonneterre[1]
[1] Centre Oscar Lambret, BP 307, F.59020 Lille Cedex; and [2]Laboratoire Bellon, Neuilly, France

Docetaxel is a new taxoid antineoplastic agent with clinical efficacy especially in breast cancer. One of the most distressing side-effects induced by docetaxel is alopecia. We studied the prevention of alopecia by using a cold cap in 98 patients receiving 100 mg/m² docetaxel by 1 h i.v. infusion every 3 weeks. One patient was lost to follow-up. 83 patients (86%) were evaluated as a success to the cold cap, as they presented WHO grade alopecia

≤ 2 and no need to wear a wig. 14 patients (14%) had to wear a wig; among them, 7 patients withdrew before the evaluation at three cycles. The cold cap is a very effective technique with minimal side-effects for docetaxel-treated patients.

Key words: alopecia, chemotherapy, toxicity

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Introduction

DOCETAXEL (TAXOTERE) is a new antineoplastic agent from the taxoid family, which promotes the assembly of microtubules, stabilizing them and preventing their depolymerisation. Several phase II trials have demonstrated that this drug has significant and consistent anti-tumor activity in metastatic breast and non-small-cell lung cancers. It has also produced significant results in other tumors among which include ovarian cancer [1, 2]. Currently, the recommended dose of docetaxel for phase II or III studies is 100 mg/m² administered as a 1-h i.v. infusion repeated every 21 days. Phase I trials have demonstrated the toxicity of docetaxel: dose-limiting neutropenia, paresthesias, asthenia, oral mucositis, fluid retention, nail changes and alopecia [1]. Alopecia is common at doses higher than 55 mg/m², and has been observed in over two-thirds of patients at doses higher than 70 mg/m² during phase I trials [1]. Alopecia occurs in over 80% of patients receiving docetaxel at the dose of 100 mg/m² [3] and represents a major psychological drawback for the patients, especially for women. Although mostly transient, alopecia is one of the most distressing side-effects of anticancer chemotherapy. In a study on patient perception of the side-effects of chemotherapy, patients chose alopecia as the second worst physical side-effect after nausea and vomiting [4]. Another study showed that 88% of the women who received pre-operative chemotherapy for breast cancer considered alopecia the most burdensome aspect of the treatment [5]. Hair loss can induce a negative body image, alter interpersonal relationships, reduce the quality of life and generated enough anxiety to cause some patients to reject potentially curative treatments, particularly women.

In our day-care hospital, the prevention of alopecia is an important endpoint for nurses and physicians. We use the cold cap for the prevention of anthracyclin-induced alopecia: 85% of female patients have no, minor or moderate alopecia and they do not need to wear a wig or a hat [6]. Due to differences in chemotherapy administration schedules (10-min bolus for epirubicin versus 1 h for docetaxel), the research nurses modified the cold cap technique and adapted it to docetaxel chemotherapy [1]. Preliminary results showed good protection from hair loss in 39 patients receiving docetaxel 100 mg/m² for metastatic breast cancer as second- or third-line chemotherapy. 21 patients had no alopecia, grade 1 was observed in 15 patients, grade 2 in two patients, and one patient had grade 3 alopecia, who had to wear a wig [7].

The following study reports the full data which confirm these promising results and promotes the cold cap safety and efficacy for the prevention of docetaxel-induced alopecia.

Patients and Methods

All patients were treated as out-patients. 98 patients received docetaxel alone (100 mg/m² i.v., every 21 days) after failure of one or more previous chemotherapy regimen during a compassionate use program or ongoing clinical trials from April 1992 to October 1995.

Patients were offered a cold cap technique aimed at the prevention of docetaxel-induced alopecia and were informed by the oncologists. The patients (93 females and 5 males) received docetaxel chemotherapy for metastatic breast cancer (n=88), advanced ovarian cancer (n=3) and advanced pancreatic cancer (n=7). Previous chemotherapy regimens were either epirubicin-based or contained mitoxantrone, vinorelbine, cisplatin, cyclophosphamide or 5-fluorouracil. Some patients had previously worn a cold cap or had already experienced hair loss during their cancer treatment.

Patients were ineligible if they had scalp metastases, prior radiation to the scalp, presence of baldness or significant hair loss. Clinical and biochemical signs of liver metastases or impairment of the liver function were recorded at admission. Patients with transaminase enzyme levels below 2.5 times the upper normal limit were eligible to receive docetaxel chemotherapy. Patients with significant liver metastases were eligible for docetaxel chemotherapy and cold cap if they had only a minor impairment of their liver function.

Scalp hypothermia was achieved with the Spenco Hypothermia Cap filled with cryogel. The cold cap was placed in the freezer for a minimum of 12 h prior to use. The temperature of the cap had to be below -25°C. First, a wet single-use mobcap was placed on the patients' hair. To apply the cap as tightly as possible, it was kept in place by bandages wrapped around the head. Cotton protected the nape, forehead and ears. The cold cap was applied 15 min. before the administration of docetaxel and left in place for 30 min. after the beginning of the infusion; then the second cap was worn for 45 min. Two cold caps were successively used (45 min. for each); the cap changing was done quickly by two nurses. To improve the hair protection, the research nurses gave some advice to the patients: no hair brushing during the treatment day, no shampoo for one week, no permanent wave or hair coloring during chemotherapy treatment, and to have a short haircut. This was done every time the patient received docetaxel. The patients were followed and treated until they either stopped receiving docetaxel, or had total hair loss.

Measurement of the degree of hair loss was determined by the nurse. Alopecia was assessed before each docetaxel cycle and during at least three consecutive cycles. 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 but reversible hair loss; grade 4, complete and irreversible alopecia).

Success was defined as WHO alopecia grade ≤ 2 and no need to wear a wig, according to patient's decision. If the patient wore a wig whatever the grade of alopecia, this was considered a failure.

Results

98 patients received docetaxel chemotherapy in combination with the cold cap. All patients but one were able to be evaluated for the results; one patient was not able to be evaluated, as she refused to continue chemotherapy and was lost to follow-up. The median age was 49 years (range 29-73). The median number of previous chemotherapy regimens was 2 (range 0-5). 83 female patients had previously received epirubicin-based regimen as adjuvant or metastatic treatment. All patients except one received at least 3 docetaxel chemotherapy cycles, the median number was 5 cycles (range 2-11).

The results are shown in Table 1. 14 (14%) patients were evaluated as a failure to the cold cap: 7 of them refused to go on through the three cycles with the caps (one at cycle 1, two at cycle 2 and 4 at cycle 3); the other 7 patients had to wear a wig, 3 had presented with grade 2 alopecia and 4 patients had grade 3 alopecia. 83 (86%) patients were successful responders to the cap as they had both grade ≤ 2 alopecia and did not need to wear a wig.

When considering prior treatment, 83 out of the 97 patients able to be evaluated had previously received anthracyclin-based chemotherapy (mostly epirubicin). Information on the results of alopecia prevention (with a cold cap) at the time of anthracyclin chemotherapy was available for 50 of these patients: 20 grade 0, 20 grade 1, 9 grade 2, 1 grade 3, and no grade 4. These same patients had the following results for docetaxel-induced alopecia prevention: 25 grade 0, 15 grade 1, 6 grade 2, 4 grade 3 and no grade 4. 14 patients had not previously received an anthracyclin-based regimen, and their results of docetaxel-induced alopecia prevention were 3 grade 0, 5 grade 1, 4 grade 2, and 2 grade 3.

The cold cap was well tolerated. Its side-effects were mild headaches and unpleasant cold sensations. Only 7 patients refused to go on with the cold cap (ad were considered as failures): 5 complained of headaches and 2 were not satisfied because of hair thinning. None of the patients treated with scalp hypothermia developed scalp metastases, with a median follow-up after the end of the treatment of 9 months (range 4-12).

Discussion

Despite the fact that alopecia is one of the most common side-effects of chemotherapy, especially with anthracyclins and taxoids, with a major social and psychological impact, relatively few trials evaluating different prevention approaches have been reported. A literature review has recently been published [8]. Four studies showed failure of hair loss prevention, but most series showed good hair preservation in 50-80% of patients with a scalp-cooling method. Several techniques were used to induce hypothermia: simple bags with crushed ice or frozen cryogel packs, caps containing cryogel and an insulation layer, caps connected to a cooling device using air or fluid and equipped with a thermostat [8]. Our studies, conducted with the Spenco Hypothermia Cap, containing cryogel, gave good hair preservation (between 80 and 85% with epirubicin 50 mg/m² and docetaxel 100 mg/m²).

The rationale for the use of cold caps is that scalp hypothermia causes cutaneous vasoconstriction with a reduced blood flow, leading to a reduction in the quantity of drugs reaching the hair follicles [9]. The pharmacokinetics of docetaxel fit a tri-exponential curve; the α, β, and γ half-lives with a 115 mg/m² 1-h infusion are 4 min., 36 min., and 22 h, respectively [1]. This means that the drug is present at high concentrations in the capillary circulation for a duration which is shorter than that of hypothermia. Cellular uptake by the hair follicles may also be reduced because of the lower temperature [10]. finally, a reduction in the metabolism of local tissue, in response to low temperature rather than reduced blood flow, is the most significant factor in preventing alopecia [8, 11].

Limited data are available on the degree of the cooling temperature that must be obtained. Hair conservation could be obtained when scalp temperature is reduced to a level ≤ 24°C [12] or < 22°C [10]. In our experience, assessment of scalp hypothermia was not done. Clinical experiences have revealed that hair preservation is improved when the temperature of the cap is around -25°C after remaining at least 12 h in the freezer. The cold caps are always placed in the freezer on the evening prior to use. A cap is used only once per day.

The precooling time ranges from 5 to 20 min. (15 min. in our study) [8]. Most of the reviewed series use a post-injection cooling time of 30 min. (range 15-60) probably taking the doxorubicin pharmacokinetics as their guidelines [8]. The post-injection cooling time with docetaxel (1-h infusion) was 15 min. in our study.

Various chemotherapy drugs have been used, with several dosages, to evaluate the efficacy of the cold cap. The degree of protection against alopecia is both drug and dose-dependent. Scalp hypothermia resulted in 100% (5/5) minor or no hair loss when a dose of < 50 mg. [11]. Our experience shows the same difference between the FEC 50 regimen (epirubicin 50 mg/m², 5-fluorouracil 500 mg/m², cyclophosphamide 500 mg/m²) and the FEC 100 regimen (epirubicin 100 mg/m²) in larger studies. Hair preservation (alopecia grade ≤ 2 and no wig) was 85% (64/73) with the cold cap during FEC 50 chemotherapy and fell to 64% (25/39) with FEC 100 chemotherapy and increased epirubicin doses (J. Bonneterre, Centre Oscar Lambret, France). No evident difference seems to exist between the results obtained in the prevention of epirubicin-induced alopecia and docetaxel-induced alopecia: 85% hair preservation was achieved in both series. In addition, previous epirubicin treatments do not seem to decrease the efficacy of the cold cap in the prevention of docetaxel-induced alopecia.

Most physicians recommend that the cold cap should not be used in haematological malignancies or solid tumors which could spread to the scalp. One study reported scalp recurrence in a patient with mycosis fungoides who was treated with a cold cap [13]. In two series [14, 15], 5 cases of scalp metastases after cold cap use in a series of 96 patients, treated for metastatic breast cancer, were also reported. No report of scalp metastasis after the cold cap in adjuvant breast cancer chemotherapy was found in the literature [8]. In another study, no scalp metastasis was observed [11]. In our experience, we have been using the cold cap for about 15 years and no increase in the rate of scalp metastases has been observed.

The influence of liver metastases in decreasing the effectiveness of the cold cap has been raised by several authors [16, 17]; impaired liver function could reduce the excretion of the drug. There is no evidence that liver function decreased the efficacy of the cold cap. In one study [15], all patients receiving adjuvant chemotherapy had normal liver function and failed to benefit from cold caps. Conversely, despite a high rate of liver metastasis in our patients, we obtained very good hair preservation.

The cold cap is well tolerated. The side-effects are headaches, unpleasant cold sensation and occasional complaints of a 'heavy' cap [11,17]. Tolerability is very good and comparable to other studies [11-17]. Few patients refused the cold cap without having tried it, mostly because they were more anxious and fearful of losing their hair than of the temporary discomfort of the cold cap. However, 10 patients refused the cold cap during the docetaxel regimen; putting the cold cap on and changing it is a very time-consuming process for the nursing staff. In our experience, there is no necessity to measure the scalp temperature during treatment.

Other techniques to prevent chemotherapy-induced alopecia are being studied with limited success to date. A phase I trial of intracutaneous interleukin 1 to prevent cytarabine-induced alopecia showed no significant protection [18]. Minoxidil is known to induce hair growth in men with male pattern baldness. A minoxidil topical solution was not effective in the prevention of doxorubicin-induced alopecia in a placebo-controlled study [19].

Alopecia is one of the most distressing side-effects of chemotherapy. docetaxel, a taxoid with a broad range of anti-tumor activity, often induces complete and reversible alopecia. The simple technique of scalp cooling appears to be as useful in preventing alopecia induced by docetaxel as it is for epirubicin. The cold cap is safe, well accepted by patients and with no major side-effects. The cold cap can be recommended for routine use in docetaxel chemotherapy, to improve the quality of life of cancer patients.

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Multi-center Study of a Frozen Glove to Prevent Docetaxel-Induced Onycholysis and Cutaneous Toxicity of the Hand

Florian Scotte, Jean-Marc Tourani, Eugeniu Banu, Michel Peyromaure, Eric Levy, Sandrine Marsan, Emmanuelle Magherini, Elisabeth Fabre-Guillevin, Jean-Marie Andrieu, and Stephane Oudard
From the Department of Medical Oncology, Georges Pompidou European Hospital; Urology Department Cochin Hospital, Paris; and Medical Oncology Department, Poitiers, France.
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Address reprint requests to Florian Scotte, MD, Department of Medical Oncology. Georges Pompidou European Hospital, 20 rue Leblanc, 75908, Paris Cedex 15, France, e-mail; **florian.scotte@hop.egp.ap-hop-paris.fr**

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A B S T R A C T

Purpose

Onycholysis and skin toxicity occur in approximately 30% of patients treated with docetaxel. We investigated the efficacy and safety of an Elasto-Gel (84400 APT Cedex, Akromed, France) frozen glove (FG) for the prevention of docetaxel-induced onycholysis and skin toxicity.

Patients and Methods

Patients receiving docetaxel 75 mg/m2 alone or in combination chemotherapy were eligible for this case-control study. Each patient wore an FG for a total of 90 minutes on the right hand. The left hand was not protected and acted as the control. Onycholysis and skin toxicity were assessed at each cycle by National Cancer Institute Common Toxicity Criteria and documented by photography. Wilcoxon matched-pairs rank test was used.

Results

Between August 2002 and September 2003, 45 patients were evaluated. Onycholysis and skin toxicity were significantly lower in the FG-protected hand compared with the control hand (P= .0001). Onycholysis was grade (G) 0 in 89% v49% and G1 to 2 in 11 % v51 % for the FG-protected hand and the control hand, respectively. Skin toxicity was GO in 73% v41 % and G1 to 2 in 27% v 59% for the FG-protected and the control hand, respectively. Median time to nail and skin toxicity occurrence was not significantly different between the FG-protected and the control hand, respectively (106 v 58 days for nail toxicity; 57 v 58 days for skin toxicity). Five patients (11 %) experienced discomfort due to cold intolerance.

Conclusion

FG significantly reduces the nail and skin toxicity associated with docetaxel and provides a new tool in supportive care management to improve a patient's quality of life.
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INTRODUCTION

Docetaxel and paclitaxel are part of the taxane group, which has emerged as one of the most powerful classes of chemotherapeutic agents and exhibits a wide range of activity against a variety of solid tumors. 1-4 Taxanes act by disrupting the normal microtubule network essential for mitotic and interphase cellular functions.5 In general, the toxicity profile of each taxane is predictable and can be managed with prophylactic measures and supportive care.6 Cutaneous toxicity manifested as erythema and desquamation of the skin of the extremities (hand-foot syndrome [HFS]) and nail changes have been reported with taxane treatment, but both toxicities have been associated more frequently with docetaxel.7-9 Although HFS does not appear to be a common adverse event with docetaxel treatment,7 a recent review of published studies by Minisini et al8 showed that the overall incidence of taxane-induced nail changes is as high as 44%.

Frozen Glove to Prevent Nail Changes

Nail changes include hyperpigmentation, splinter hemorrhage, subungual hematoma, subungual hyperkeratosis, orange discoloration, Beau-Reil lines (indicating the cessation of nail growth), acute paronychia, and onycholysis (the loosening or separation of a fingernail or toenail from its nail bed). Usually, several or all nails are involved. Some nail changes are asymptomatic and cause only cosmetic problems, whereas others can be accompanied by either discomfort or pain, and negatively affect a patient's ability to perform manual activities and ambulate. Nail changes are usually transitory and disappear with drug withdrawal, but may persist in some patients.10 Application of local topical antibiotics or antifungal treatments may be required to treat nail bed infections, which seem to be a complication of nail's detachment. Onycholysis is manifested in 2% to 3% of patients.11 The brown discoloration associated with nail toxicity is indicative of bleeding beneath the nails. Dermatologic examination may show no evidence that an infection was the origin of the nail change.[12] The type of nail change is related to the number of chemotherapy cycles administered, and to date no effective preventive measures are available.[13]

The Elasto-Gel flexible frozen glove.

The physiopathology of nail toxicity is unknown. Drug-induced nail abnormalities result from toxicity arising in the various nail constituents, such as the matrix, nail bed, periungual tissues, or blood vessels in the fingers.[14] Several studies have suggested that the antiangiogenic properties of taxanes may be involved in nail toxicity,[15, 16] whereas another study suggests the existence of a neurogenically mediated inflammatory process.[17]
Docetaxel-induced HFS presents as a discoloration of the skin that progresses to blisters and desquamation, and may be accompanied by nail changes that progress to onycholysis.[7] The hands are usually more frequently affected than the feet. The cause of HFS is also unknown, but it appears to be a direct cytotoxic effect on keratinocytes associated with peak drug concentrations and cumulative doses.[7,9]
Although nail and skin toxicity are not life threatening, they should be managed effectively to prevent early discontinuation of chemotherapy; the toxicities often do not

resolve between cycles. Cold temperature applied to the scalp before, during, and after chemotherapy reduces the incidence of chemotherapy-induced alopecia.[18-20] This effect is related to a cold-induced vasoconstriction, which reduces the amount of drug reaching the hair follicles, and causes a decrease in follicular metabolism. In addition, oral cryotherapy has been administered with efficacy in patients receiving bolus-dose fluorouracil therapy.[21] This concept was extended to the present study of a frozen glove (FG) for the prevention of nail and skin toxicity associated with docetaxel treatment. The primary end point was efficacy in onycholysis prevention, and secondary end points were the assessment of efficacy in the prevention of skin toxicity, the median time to occurrence of nail and skin toxicity, and patient comfort.

PATIENTS AND METHODS

Study Design

In this phase II, multi-center, matched case-control study, we evaluated the applicability and efficacy of FG therapy in the prevention ofdocetaxel-induced onycholysis and skin toxicity during a 14-month period extending from 2002 to 2003. Each patient wore the protective glove on the right hand and had no protection

Fig 2. Nail toxicity grade 2 (onycholysis) present on the left hand (control) but absent on the protected right hand.

on the left hand, which was considered to be the control side. By this method, we could obtain a comparative incidence of nail and skin disorders with and without cold protection.
Patients enrolled onto this study were undergoing treatment for a variety of tunum types with docetaxel 75 mg/m2 as a 1-hour intravenous infusion every 3 weeks either alone or in combination with other cytotoxic agents. Inclusion criteria included no prior treatment with taxanes, the absence of skin and nail disorders at the start of treatment, a life expectancy of at least 3 months, and an Eastern Cooperative Oncology Group performance status of 0 to 2. Patients were excluded if they had Raynaud's phenomenon, distal metastases, Original pathology, arteriopathy, cold intolerance, or peripheral neuropathy grade 2 or higher. All patients provided written informed consent.
Patients wore an Elasto-Gel (84400 APT Cedex, Akromed, France) flexible glove (Fig 1). This patented glove contains glycerin, which has thermal properties, allowing its use in hot or cold therapies. The gel-filled glove covers the hand to the wrist and separates the thumb from the rest of the hand. Before use, it must be refrigerated for at least 3 hours at -25 to -30°C. With every docetaxel infusion, each patient wore an FG for a total of 90 minutes on the right hand (15 minutes before the administration of docetaxel, during the 1-hour docetaxel infusion, and 15 minutes after the end of infusion). Because of the duration of the infusion, two FG's were used successively (for 45 minutes each) to maintain a consistently low temperature of the hand. The left hand was not protected by the FG and acted as the control.

Frozen Glove to Prevent Nail Changes

Onycholysis and skin toxicity were assessed at each cycle by the medical investigator (F.S. or E.L. in Paris and J.M.T. in the Poitiers centers) and assessment was repeated by a second different observer, using National Cancer Institute Common Toxicity Criteria (Version 2); that is, grade 1, indicated by discoloration, ridging (koilonychia), or pitting; and grade 2, indicated by partial or complete onycholysis or pain in the nail bed. Changes were photographically documented by the medical investigator. Patients' comfort level was assessed using a 4-point rating system that determined whether patients were dissatisfied (0), not very satisfied (1), satisfied (2), or very satisfied (3). The results were expressed as two patient groups: those satisfied with the FG (2 and 3) and those dissatisfied with the FG (0 and I). Treatment was stopped when patients showed intolerance to the FG, had a serious adverse event, or withdrew consent.

Statistical Analysis

Analyses of toxicity were carried out on the intent-to-treat population. The Wilcoxon matched-pairs rank test was used to determine the magnitude of difference between the control hands and the FG-protected hands. The Kaplan-Meier and log-rank methods were used to estimate and compare differences in time to toxicity occurrence.

RESULTS

Patients

Forty-five patients (10 women, 35 men; median age of 65 years) undergoing treatment for lung, breast, prostate, Fig 3. Nail toxicity grade 1 (dyschromia), showing the difference between the left hand (control) and the protected right hand.
and other cancers were enrolled onto the study (Table 1). Docetaxel was administered either as monotherapy (71%) or in combination with other cytotoxic drugs (29(%), such as carboplatin, vinorelbine, and anthracyclines. This was first-line chemotherapy for 76% of patients. The median number of docetaxel cycles administered was six (range, one to nine cycles) and the median cumulative docetaxel dose was 810 mg (range, 150 to 1,275 mg; Table 1).

Nail and Skin Toxicity

Forty-five patients who received docetaxel chemotherapy in combination with FG treatment were evaluated for nail toxicity. The application of FG significantly reduced the overall occurrence of nail toxicity from 51% to 11% ($P = .0001$), with grade 2 nail toxicity (onycholysis) occurring in none of the FG-protected hands compared with 22% of the control hands (Fig 2). Grade 1 toxicity (dyschromia; Fig 3) was observed in 11% of the FG-protected hands and in 29%, of the control hands (Table 2).

Forty-one patients receiving docetaxel chemotherapy in combination with FG treatment were assessed for skin toxicity; the remaining four patients presented with incomplete data. Overall, skin toxicity occurred in 24% of the FG-protected hands versus 53% of the control hands ($P = .0001$; Table 3). Although the appearance of nail toxicity was delayed with FG protection, no difference was observed in the median time to appearance of skin toxicity (Table 4).

Patient Comfort

Assessment of patients' global comfort included factors such as glove contact, temperature tolerance, and immobilization constraints. Forty-three patients were assessable (two patients refused FG protection). Using the ad-hoc rating scale, 37 patients (86%) were satisfied with the treatment, whereas six were dissatisfied, including five (11%) who withdrew from the study because of cold intolerance during glove contact (Table 5).

DISCUSSION

Chemotherapy-induced toxicity adversely affects patients' quality of life and limits the dose of chemotherapy that can be administered. The dermatologic complications of cancer chemotherapy can result in significant morbidity, cosmetic disfigurement, and psychological distress. In this study, the use of an FG reduced the incidence of nail and skin toxicity associated with docetaxel 75 Mg/m2 administered every 3 weeks, either alone or in combination with other cytotoxic agents. Eleven percent of the FG-protected hands developed nail toxicity with dyschromia, but no onycholysis; this result compared favorably with the unprotected hands, 29% of which developed dyschromia (grade 1) and 22% of which developed onycholysis (grade 2). The FG delayed the median time to occurrence of nail toxicity (106 days) compared with non-FG-protected hands (58 days). Similarly, the incidence of skin toxicity of the FG-protected hand was reduced by half. The incidence of nail changes observed in the unprotected hands in this study are consistent with those reported for docetaxel.8,11-13,22 Although taxane-induced nail toxicity has been observed in patients using the regimen administered weekly and every 3 weeks,8 the risk of developing nail reactions may be related more to the dosing interval and the cumulative dose than to the dose administered.7-9 The temperature of the FG in this study (-25 to -30°C) was in the same range as that used in a study of the cold cap to prevent docetaxel-induced alopecia,19 in which 86% of patients presented with no worse than grade 2 alopecia, and had no need to wear a wig.

In this study, the simple FG technique reduced the incidence of nail and cutaneous toxicity. The FG is easy to apply, is well accepted by most patients, and has no major adverse effects. Thus, it may be considered a new tool in supportive care and may be recommended for routine use with chemotherapy agents. These favorable results warrant additional studies to assess the efficacy of FG protection with other doses or schedules of docetaxel, either alone or in combination, and with other chemotherapeutic agents, such as free or liposomal doxorubicin.7-9,23 Future applications can also include the feet. A logical development of our study is the administration of three-fold therapy using a cold cap, gloves, and socks in a blinded manner for the investigator, and random hand and foot allocation.

In August 2004, the US Food and Drug Administration approved docetaxel for use in combination with doxorubicin and cyclophosphamide for the adjuvant treatment of patients with operable, node-positive breast cancer,24 and in May 2004, approval was obtained for the use of docetaxel in combination with prednisone as a treatment for men with hormone-refractory metastatic prostate cancer.25 In addition, docetaxel is being studied extensively in clinical trials for safety and efficacy in head and neck and gastric cancers. A new era is beginning in the field of interventional measures. Such measures might be capable of preserving the duality of life for thousand of patients.

See Also: **Journal of Clinical Onocology article - Multicenter Center of a Frozen Glove to Prevent Docetaxel-Induced Onycholysis and Cutaneous Toxicity of the Hand**

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