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Taxane-induced nail changes: Predictors and efficacy of the use of frozen gloves and socks in the prevention of nail toxicity

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A B S T R A C T

Purpose: The primary endpoint of this study was to determine predictors of taxane-related nail toxicity. The secondary endpoint was to evaluate the efficacy of the use of frozen gloves and socks in the prevention of taxane-related nail toxicity.
Methods: This descriptive, interventional, cross-sectional study was conducted with 200 patients. The patients were assigned to the frozen gloves/socks intervention group or control group. Frozen gloves/socks were applied only in hourly taxane-based treatments. The Patients Record Forms of the clinic were used in data collection. Nail changes were graded using the NCI Common Toxicity Criteria for each patient and treatment. Logistic regression analysis was performed to predict the factors that affect nail changes.
Results: The majority of the patients enrolled in the study were women diagnosed with breast cancer. The two groups were statistically similar for the cancer diagnosis, type and number of taxane cycles administered. Grade 1 nail toxicity was found in 34%, grade 2 in 11%, and grade 3 in 5.5% patients. Taxane-related nail toxicity was higher in patients who were female, had a history of diabetes, received capecitabine in conjunction with docetaxel and had breast or gynecological cancer diagnosis. Nail changes increased with an increase in the number of taxane cycles administered, BMI and severity of treatment-related neuropathy.
Conclusions: The multivariate analysis demonstrated that BMI, breast or ovarian cancer diagnosis and the number of taxane cycles administered were the independent factors for this toxicity. No statistically significant difference in nail toxicity incidence and time to occurrence of nail changes was found between the intervention and the control groups.

Introduction

The taxanes, paclitaxel and docetaxel, are effective chemotherapeutic agents used in the treatment of many malignant diseases including breast, lung, ovarian, bladder, and prostate cancer (Minisini et al., 2003). The taxane-treatment related side effects most commonly reported by patients treated with paclitaxel were myelosuppression, neuropathy, alopecia, hypersensitivity reactions and myalgias/arthralgias; for those treated with docetaxel, the most commonly reported side effects were myelosuppression, asthenia/fatigue, alopecia, skin reaction, stomatitis, hypersensitivity reactions and a fluid-retention syndrome (http://www.bms.com; http://www.sanofi-aventis.ca). Additionally, series and case reports have shown that both drugs are associated with nail changes in up to 44% of the patients (Minisini et al., 2003). It has been reported that taxanes cause nail changes more frequently than other drugs (Gilbar et al., 2009; Marrs and Newton, 2004; Minisini et al., 2003). Some nail abnormalities, such as dark pigmentations and Beau's lines on the nail, are asymptomatic and are a cosmetic nuisance (Marrs and Newton, 2004). However, others such as sub-lingual hemorrhage, transverse loss of the nail plate, acute painful paronychia and onycholysis, can affect the quality of life of the patients causing discomfort, pain and impairment to activities of daily living (Baker et al., 2009; Gilbar et al., 2009; Minisini et al., 2003). Nail changes are usually transitory and disappear with drug withdrawal but may persist in some patients (Scotté et al., 2005). The physiopathology of nail toxicity is unknown. Several studies and case reports have suggested that the cumulative dose and the weekly administration of taxanes may be involved in an increased incidence of nail toxicity (Gilbar et al., 2009; Honget al., 2007; Almagro et al., 2000; Wasner et al., 2002; Winther et al., 2007).

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In general, the toxicity profile for each taxane is predictable and can be managed with prophylactic measures and supportive care (Baker et al., 2009; Scotté et al., 2005). Management of the nail toxicity involves counseling patients regarding the potential for nail toxicity, providing practical strategies (nail cutting, avoiding potential irritants) for prevention, and instituting appropriate treatment (topical or oral antimicrobials, possibly cessation or dose reduction of the offending agent) when necessary (Gilbar et al., 2009). Hussain et al. (2000) suggests that patients avoid sunlight to prevent the nail changes from worsening. Another method to prevent or reduce nail changes is to use cooling according to a similar principle used in cold caps to prevent alopecia. Cold causes vasoconstriction, thus reducing blood flow to the area and reducing the amount of drug reaching the nail structures. Scotte et al. (2005) investigated the use of a frozen glove on one hand of patients 15 min before, during and 15 min after treatment with docetaxel. It was reported that the use of the frozen glove prevented cases of grade 2 onycholysis (according to the common toxicity criteria version 2.0) and increased the time until occurrence of nail toxicity (Scotté et al., 2005). A similar study was conducted to assess the efficacy and safety of a frozen sock for the prevention of docetaxel-induced nail toxicity (Scotte et al., 2008). The application of the frozen sock significantly reduced the incidence of nail toxicity, with grade 1–2 toxicity not occurring in the patients whose feet were protected by a frozen sock compared with 21% occurrence in the patients whose feet were unprotected. Onycholysis occurred in 2% of patients whose feet were unprotected.

A literature review revealed that many factors affect nail toxicity and that cryotherapy is the first proven measure used effectively to prevent nail toxicity. Thus, the primary endpoint of this study was to determine the predictors of the taxane-related nail toxicity in our patient group. The secondary endpoint was to evaluate the efficacy of the use of frozen gloves/socks in the prevention of taxane-related nail toxicity.

Methods

A descriptive, interventional, prospective study was performed between 2005 and 2010 in the outpatient clinic of the Adnan Aydiner Oncology Center, Istanbul, Turkey. Criteria for the inclusion of patients were as follows: patients diagnosed with any type of cancer who were receiving adjuvant or metastatic chemotherapy containing paclitaxel or docetaxel administrated hourly for first time (if prior therapy without taxane had been completed more than 6 months before the study entry); older than 18 years of age; able to read, write, and communicate in Turkish; a primary school education; and consenting to participate in the study. Eastern Cooperative Oncology Group performance status (ECOG PS) of 0, 1 or 2 was required for study participation. The patients who had a social or psychological state that would interfere with participation in the study or those who did not want to participate in the study after it was explained to them were not included in the study. The data of the patients who had received taxane-containing therapy for fewer than three cycles were excluded. Approximately 3000 patients were admitted to the clinic between the years 2005–2010 for treatment. The annual patient numbers reflecting the inclusion criteria of the study were 14, 33, 40, 56, 32 and 25, for year 2005, 2006, 2007, 2008, 2009 and 2010, respectively. In our study, all 200 patients were included. This study was approved by the administration of the Oncology Institute of Istanbul University.

At the first treatment the patients were informed and a verbal consent was obtained. Then patients were assigned to the frozen gloves/socks intervention group or control group. Patients who were prescribed an hourly taxane infusion and elected to received cold application during treatment, following a detailed explanation of the potential benefits, were assigned to the cryotherapy (frozen glove and sock) ($n = 55$) group. However, patients who received 3-h taxane infusions or did not want cold application during treatment were assigned to the control ($n = 145$) group. Patient education about specific interventions that may help to reduce the risk of nail toxicity was provided to all patients. Patient education of the management of the nail toxicity involved counseling patients on the potential for nail toxicity, providing practical strategies (nail cutting, avoiding potential irritants) for prevention, and instituting appropriate treatment (topical or oral antimicrobials, cessation or dose reduction of the offending agent) when necessary. Frozen gloves/socks were applied to patients who received hourly taxane-based chemotherapy. During the 1-h taxane infusion, patients wore Elasto-Gel (Cedex, Akromed, France) flexible gloves and socks for a total of 90 min (15 min before the administration of taxane, during the 1-h taxane infusion, and 15 min after the end of infusion). These patented gloves and socks contain glycerin, which has thermal properties, allowing its use in hot or cold therapies. Before use, they are chilled for at least 3 h at −18 to −20 °C. During each treatment, four pairs of gloves/socks were used successively (for 20–30 minutes each) to maintain a consistently low temperature of the hand/foot. Nail toxicity was assessed for each cycle of the treatment on day 1 for all 3–4 week regimens according to the National Cancer Institute criteria (NCI-CTCAE) version 3 as follows: grade 1, indicated by discoloration, ridging (koilonychia), or pitting; grade 2, indicated by partial or complete onycholysis or pain in the nail bed; and grade 3, indicated by interfering with activities of daily living. Time to occurrence of the nail changes was calculated from the date of initiation of therapy to the day the toxicity was first noticed. Treatment related quality of life [QOL] of the patients was assessed for each cycle of the treatment on day 1 for all 3–4 week regimens using The Chemotherapy Symptom Assessment Scale. This scale developed by the researches is part of the Patients Record Forms of the clinic and is a likert type QoL scale includes 20 symptoms frequently reported by the patients during chemotherapy. The severity of symptoms experienced after treatment was quantified using 5 possible numeric responses, where 0 = not at all, 1 = a little bit, 2 = somewhat, 3 = quite a bit and 4 = very much. These 20 items was used to calculate the QOL score of the patients. Higher score indicating worse symptom experience and bad QOL.

Statistical analysis

The SPSS version 7.5 (SPSS, Chicago, Ill) program was used for data analysis. Descriptive statistics, means, median, frequencies, and percentage were used to show the distribution of the sociodemographic and the illness or treatment-related characteristics of the patients. Comparisons were made using the Chi-square tests, the Mann–Whitney *U* test and the Kruskal Wallis test. The relationships were evaluated with Spearman's rho correlations. To examine the impact of clinical and treatment variables on the incidence of nail toxicity, logistic regression analysis was used. For all statistical analyses, a 2-sided p value of less than 0.05 was considered statistically significant.

Results

Patients' characteristics and findings related to patient's disease

Most of the patients were women with breast cancer diagnosis. The mean age of the study group was 52.79 ± 11.41 years (range 22–77 years), and the mean BMI was 28.38 ± 5.05 (range 17–48). However, there was no statistically significant difference between