Management and Outcome of Taxane-Induced Nail Side Effects: Experience of 79 Patients from a Single Centre

Aurora Alessandrini Michela Starace Giulia Cerè Nicolò Brandi
Bianca Maria Piraccini

Division of Dermatology, Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, Bologna, Italy

Keywords

Nail side effects · Taxane · Chemotherapy · Breast cancer · Hemorrhagic onycholysis

Abstract

Background: Nail changes are a common side effect of taxane chemotherapy, although their correct management is poorly standardized. **Objective:** To evaluate incidence, clinical aspects, and response to treatment of taxane-induced nail side effects in patients treated with taxanes for malignancies. **Patients and Methods:** We performed a retrospective clinical study of 79 patients with taxane-induced nail changes from January 2015 to July 2018. **Results:** Paclitaxel was the most responsible drug and both hands and feet were often affected (46.8%). Grade 2 nail toxicity was seen in 63.3% of the patients, including painful subungual hematoma, hemorrhagic onycholysis, and paronychia. Grade 3 nail toxicity was seen only in 2.5% of the patients, including hemorrhagic onycholysis and pyogenic granuloma. Removal of the detached nail plate with application of topical antibiotics and steroids induced regression of symptoms within 2 weeks. **Conclusions:** Nail toxicity develops mostly at the end of therapy, and total drug dosage is the only known fac-

tor that predisposes to these side effects. Trauma possibly plays a role as the most severe signs are located on the great toenails. Although it is impossible to prevent taxane-induced nail side effects, a careful patient monitoring permits to immediately recognize and manage the symptoms in order to induce their remission and improvement of the patient's quality of life.

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Introduction

Taxanes are anticancer drugs widely prescribed in chemotherapy regimens for the treatment of numerous neoplasms, both in polychemotherapy and in monotherapy, mostly in metastatic cases. Taxanes represent one of the most active pharmacological classes in the treatment of solid neoplasms such as breast, lung, ovarian, prostatic, and gastric carcinomas [1]. Nail changes are a common side effect, although correct information about their proper management is lacking [2–4].

Our study evaluated the incidence, clinical aspects, severity, and response to treatment of taxane-induced nail side effects in a group of patients that have been visited in

Fig. 1. Grade 1 (G1) nail toxicity: nonhemorrhagic onycholysis (a); nonpainful subungual hematomas (b); hematomas and melanonychia (c).

our outpatient consultation for nail disease of the Dermatology Unit, Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, Italy, from January 2015 to July 2018.

Materials and Methods

Since January 2015, we established a weekly consultation for patients of the Oncology Department of the University of Bologna experiencing nail lesions during treatment with taxanes and other chemotherapeutic agents. For each patient, we collected clinical data from oncologic medical records, including general information, type, site and stage of the tumor, oncology therapy (if performed) prior to taxanes, type of taxane therapy and dose (in mg/m²), staging/therapy ratio (neoadjuvant, adjuvant, advanced I–II–III line), and chemotherapy cycle in which nail side effects occurred. Then, we analyzed location (hands, feet, or both) and type of nail side effects, assessing their severity on the basis of the criteria reported by the National Cancer Institute [5] and classifying the patient's nail toxicity in grades 1, 2, and 3. Grade 1 (G1) nail toxicity included the following nail signs: color alterations due to hematomas or melanonychia, Beau's lines, nonhemorrhagic onycholysis, and mild paronychia (Fig. 1). Grade 2 (G2) included painful hemorrhagic onycholysis and moderate-to-severe paronychia, associated with pain and/or impaired function (Fig. 2). Painful hemorrhagic onycholysis with seropurulent discharge and/or infection, or with paronychia associated with pyogenic granulomas or nail bed pyogenic granulomas were defined as grade 3 (G3).

Once taxane-induced nail toxicity was diagnosed and its grade defined, patient therapy and follow-up were established, as summarized in Table 1. All patients with subungual hematoma were prescribed daily soaking of the affected nail in antiseptic solution, and follow-up after 15 days was set to check the possible development of onycholysis. Cutting off the detached nail plate was performed in all nails with onycholysis, using a nail clipper. This allowed observation of the nail bed and a better staging of the side effect severity. The nail bed epithelium was normal in simple onycholysis (G1), eroded in hemorrhagic onycholysis (G2), covered with purulent exudate when infection was present, or presenting with a pyogenic granuloma in G3. Removal of the detached nail plate with exposition of the nail bed also allowed the application of topical therapy on it. In case of nail pyogenic granuloma, mechanical removal with curettage was performed. The first follow-up visit was set after 15 days, and the second at a distance of 1 or 2 months, depending on the outcome of the lesions.

Results

Patients' demographics and clinical characteristics are summarized in Table 2. A total of 1,059 oncological patients were prescribed with taxane chemotherapy from January 2015 to July 2017 in the Oncology Department of the University of Bologna, but only 79 of them (7.5%) were referred to our outpatient consultation complaining of nail toxicity during treatment. They were all

Fig. 2. Grade 2 (G2) nail toxicity: painful subungual hematomas (a); hemorrhagic onycholysis and Beau's lines (b); hemorrhagic onycholysis and moderate paronychia (c).

Table 1. Standard therapy related to the degree of nail toxicity

Grade	Nail symptom	Therapy	Follow-up
G1	Melanonychia	No therapy	None
	Beau's lines	No therapy	None
	Splinter hemorrhages	No therapy	None
	Subungual hematoma (not painful)	Daily soaks with antiseptic solution	After 15 days in order to evaluate development or not of onycholysis
G2	Nonhemorrhagic onycholysis	Cutting the onycholytic nail plate	None
	Painful subungual hematoma	Systemic paracetamol up to 3,000 mg/day Daily soaks with antiseptic solution	After 15 days in order to evaluate development or not of onycholysis
	Hemorrhagic onycholysis	Cutting the onycholytic nail plate Daily soaks with antiseptic solution Application of fusidic acid and betamethasone valerate cream	After 15 days
	Mild-to-severe paronychia	Application of betamethasone valerate cream	After 15 days
G3	Painful onycholysis with seropurulent discharge	Cutting the onycholytic nail plate Daily soaks with antiseptic solution Application of fusidic acid and betamethasone valerate cream Systemic azytrhomycin 500 mg/day for 3 days	After 15 days
	Painful paronychia with periungual pyogenic granuloma	Curettage Application of fusidic acid and betamethasone valerate cream	After 15 days
	Subungual pyogenic granuloma	Cutting the onycholytic nail plate Curettage Application of fusidic acid and betamethasone valerate cream	After 15 days

Table 2. Epidemiological and clinical data related to patient population studied between January 2015 and July 2018

<i>Patients treated with taxanes who developed nail toxicity</i>	
Females	98.7% (78/79)
Males	1.3% (1/79)
Average age, years	58.3
<i>Primary tumor location</i>	
Breast	84.8% (67/79)
Ovary	11.4% (9/79)
Endometrium	1.3% (1/79)
Prostate	1.3% (1/79)
Stomach	1.3% (1/79)
<i>Taxane regimen</i>	
Paclitaxel	88.6% (70/79)
Weekly taxol	90.0% (63/70)
Carbo-taxol	8.6% (6/70)
Adriamycin taxol	1.4% (1/70)
Docetaxel	11.4% (9/79)
Taxotere 100	66.7% (6/9)
Weekly taxotere	22.2% (2/9)
Carbo-taxol	11.1% (1/9)
Monotherapy	64.6% (51/79)
Polytherapy	35.4% (28/79)
Average dose of taxanes, mg/m ²	84.4
Average number of taxane administrations	14.7
<i>Nail toxicity</i>	
Grade	
G1	34.2% (27/79)
G2	63.3% (50/79)
G3	2.5% (2/79)
Anatomical site	
Hands	11.4% (9/79)
Feet	41.8% (33/79)
Hands and feet	46.8% (37/79)
Time of onset	
Beginning phase	9.0% (7/79)
Middle phase	23.0% (18/79)
Ending phase	68.0% (54/79)

Caucasians, 78 females (98.7%) and 1 male (1.3%), with and an average age of 58.3 years (ranging from 84 to 28 years). The primary tumor location was the breast in 67 (84.8%), followed by ovary (9/79, 11.4%), endometrium (1/79, 1.3%), prostate (1/79, 1.3%), and stomach (1/79, 1.3%). Among the 67 cases of primary tumor localized in the mammary gland, 3 patients were affected by ductal carcinoma in situ (4.5%), 59 by an infiltrating ductal carcinoma (88.1%), 4 by an infiltrative lobular carcinoma (6.0%), while 1 patient had another type of breast tumor (1.5%). According to the histotype, among the 9 patients with ovarian carcinoma, 3 were affected by an endometrioid adenocarcinoma (33.3%) and 6 by a papillary se-

rous carcinoma (66.7%). As for the remaining patients, the one who had a primary tumor localized in the endometrium was affected by a stage IIIC endometrial adenocarcinoma, the one who had a primary tumor localized in the prostate was affected by a stage III adenocarcinoma, while the one who had a primary tumor localized in the stomach was affected by a stage III adenocarcinoma.

Paclitaxel was responsible for nail changes in 70 patients (88.6%): 63 of them received a weekly treatment with taxol, 6 a combined treatment with carbo-taxol, and 1 with adriamycin taxol. The remaining 9 patients (11.4%) were treated with docetaxel: 6 with taxotere 100 formulation, 1 with carbo-taxol, and 2 with weekly taxotere. At the moment of the nail toxicity diagnosis, 51 patients received a single therapy with taxanes (64.6%), while 28 patients were on polytherapy (35.4%). The most frequently administered chemotherapeutic dose was 80 mg/m² (56/79, 70.9%), generally prescribed for 12 consecutive weeks (42/79, 53.2%). The average dose of taxanes administered to every patient was 84.4 mg/m² (range 35–175), and the average number of taxane administrations for every patient was 14.7 (range 4–46).

Taxane nail side effects involved both hands and feet in most of the cases (37/79, 46.8%), exclusive fingernails involvement was seen in 9 patients (11.4%), while exclusive toenails involvement was detected in 33 (41.8%). Exclusive grade 1 nail toxicity due to taxanes was seen in 27 patients (34.2%), with the following symptoms: Beau's lines ($n = 4$), melanonychia ($n = 2$), splinter hemorrhages ($n = 12$), nonpainful subungual hematomas ($n = 10$), and nonhemorrhagic onycholysis ($n = 8$). Grade 2 nail side effects were seen in 50 of 79 patients (63.3%) and presented as painful total subungual hematoma ($n = 6$), painful hemorrhagic onycholysis ($n = 44$), and moderate-to-severe painful paronychia ($n = 2$). Grade 3 taxane nail toxicity was seen in 2 patients (2.5%), who presented with hemorrhagic associated with pyogenic granuloma.

More than one side effect was often observed in the different nails. Nail alteration grading correlated with the anatomical site involved as follows: 5 patients (6.3%) had an exclusive G1 fingernail toxicity, 4 patients (5.1%) had an exclusive G2 fingernail toxicity, 10 patients (12.7%) had an exclusive G1 foot nail toxicity, 21 patients (26.6%) had an exclusive G2 foot nail toxicity, and 2 patients (2.5%) had an exclusive G3 foot nail toxicity; 13 patients (16.5%) had a G1 concomitant hand and foot involvement, and 24 patients (30.4%) had a G2 concomitant hand and foot involvement.

A total of 17 of the 27 patients with G1 nail toxicity were on single therapy (63%) and 10 on polytherapy (37%), 33 of the 50 patients with G2 nail toxicity were on single therapy (66%), and 17 on polytherapy (34%), 1 of the 2 patients with G3 nail toxicity was on single therapy (50%), and 1 on polytherapy (50%). As regards the onset of nail alterations in relation to the taxane chemotherapy administration cycle, 7 patients (9%) developed nail side effects at the beginning of taxane therapy, 18 patients (23%) had the first symptoms during the midtreatment, and 54 patients (68%) experienced nail side effects at the end of chemotherapy.

Follow-up was not required in 7 patients (8.9%) because they had simple nail alterations at the moment of diagnosis. Only 3 of the 72 patients (91.1%) who underwent a follow-up visit after 2 weeks still presented with painful toenail bed erosion and necessitated prolongation of topical therapy, while the other 70 patients experienced gradual remission of the painful nail changes within 15 days from our visit. None of the patients had to discontinue taxane therapy or to lower its dosage.

Discussion

Taxanes are one of the most active pharmacological classes in the treatment of solid neoplasms such as breast, lung, ovarian, prostatic, and gastric carcinomas. However, the efficacy of treatment regimens of solid tumors with docetaxel and paclitaxel is burdened by the development of important side effects, sometimes of such magnitude to permanently interrupt the use of these pharmacological classes, thus worsening the patient's prognosis. Among the most common side effects, there are gastrointestinal, hematological and neurological toxicity, hypersensitivity reactions, water retention, anorexia, hair loss, and nail alterations.

Reports of nail side effects due to taxanes reveal the same type variety of alterations: asymptomatic onycholysis secondary to paclitaxel [6, 7], subungual abscess from docetaxel [8], and purple nail bed with onycholysis associated with the administration of paclitaxel [9]. Nail matrix side effects, as Beau's lines and melanonychia, are probably not published as not painful and therefore not leading to discontinuation of therapy or to dosage reduction. Indeed, the most common side effects due to taxanes involve the nail bed and consist of hemorrhages and onycholysis. Direct damage to the blood vessels or drug-induced thrombocytopenia predispose to the development of hemorrhages, while a direct toxic effect of taxanes on

Fig. 3. Cutting the detached nail plate (a) is mandatory in onycholysis in order to explore and verify the presence or not of pyogenic granuloma and nail bed erosion (b).

the nail bed induces nail detachment [10]. Some authors [11] suggested that the integrity of peripheral nerve fibers is necessary for the development of taxane-induced nail abnormalities. Two neurotropic mechanisms can be postulated: release of neuropeptides as a consequence of the activation of the nociceptive C fibers, or the release of prostaglandins from postganglion fibers of the sympathetic system. A case of taxane nail alterations improved by cyclooxygenase-2 inhibitors has been described [11], supporting the second hypothesis.

Whatever the pathogenesis, nail bed symptoms due to taxanes may present with a different degree of severity: onycholysis caused by taxanes can, in fact, be painful or not, and associated or not with erosions of the epithelium or pyogenic granulomas. Nail bed hemorrhages can be so severe to involve several nails and be associated with severe pain.

Interesting data emerged from our study. First of all, from January 2015 to July 2018, the estimated incidence of taxane-induced nail toxicity among oncological patients was 7.5%. This prevalence is possibly lower than in reality, as we visited only patients who reported nail signs, especially when associated with pain or cosmetic discomfort, and not those who did not mention the side effect to the oncologist. In fact, we believe that the 27 patients (34.2%) with G1 toxicity do not represent the real prevalence of the condition, but are actually a small part of it, representing “the tip of the iceberg.” In most of the cases (63.3%), taxane-induced nail side effects were graded as G2 toxicity. Grade 2 nail side effects were always rather mild and regressed within 2 weeks after correct management. The feet were more frequently affected than the hands (41.8 vs. 11.4%), although most of the patients presented simultaneous involvement of hands and feet

Fig. 4. Proposed algorithm for management of patients with taxane nail toxicity.

(46.8%). There is no specific targeted digit, thus emphasizing the stochastic and absolutely unpredictable trend of nail alteration, both in terms of location and gravity. G3 toxicity cases were rare in our series (2 patients, 2.5%).

The average age of patients experiencing taxane-induced nail changes was 58 years (range 28–84), suggesting that nail toxicity affects mainly the adult population; however, this evidence is probably distorted by the fact that the malignancies we reported mostly affect the adult population, saving the younger age group. The most common underlying oncological disease was infiltrating ductal carcinoma in different stages, even though with stage I (19 patients), stage II (22 patients), and stage IV (11 patients) prevalence. The most frequently administered drug as well as the most responsible for nail toxicity was paclitaxel; 51 patients (64.6%) developed nail toxicity after treatment with taxanes only, while 28 patients (35.4%) after receiving polychemotherapy. The most frequently administered chemotherapeutic dose of taxanes was 80 mg/m² (56/79, 70.9%). The most often administered treatment dose in the studied population was 80 mg/m² for 12 consecutive weeks (42/79, 53.2%).

As the average number of taxane administrations per patient was 14.7, most of the patients (68.4%) showed nail toxicity between the 9th and the 12th therapy cycle, probably due to a nail storage disorder [10]. Only 9% of patients showed nail toxicity at the beginning of the treatment and 23% during the midtreatment. Therefore, the only risk factor for the development of taxane-induced nail changes is the overall duration and the frequency of the therapy (the patients with the most severe symptoms

were those with weekly administrations of taxanes). Thus, the development of nail alterations is strongly associated with the number of chemotherapy cycles, and it increases with the taxane cumulative dose.

Management of taxane nail side effects firstly includes grading of severity. Recognition of painful subungual hematoma or painful onycholysis indicates grade 2 severity. These patients should be treated as follows: for painful subungual hematoma, there is no way to avoid development of onycholysis, which usually appears after 10–15 days and treatment should be waited for to avoid superinfection by daily soaking of the digits in antiseptics. Meanwhile, pain can be reduced by the intake of a COX2 inhibitor [12]. For painful onycholysis, cutting the detached nail plate is mandatory to explore and treat the nail bed. The epithelium can be normal, eroded, or present pyogenic granuloma (Fig. 3a, b). Granuloma curettage and topical therapy with antibiotics and corticosteroids induce remission in almost all cases within 15 days, more days of cure being necessary in a minority of patients.

Conclusions

Our study suggests that although the incidence of nail alterations is high among taxane-treated patients (7.5%), there is a significant underreporting of these changes in oncology studies, probably due to milder and unpainful symptoms occurring in most of the patients that do report them. Most of the patients with taxane-induced nail changes develop them at the end of therapy, and total

drug dosage is the only known factor that predisposes to nail side effects. Trauma possibly plays a role as the most severe signs are located on the feet, especially the great toenails.

Currently, the only way to prevent taxane nail side effects is represented by the use of frozen gloves or socks [13–15], but, as in our case series, these medical aids are not always available; thus, a careful patient monitoring is essential to immediately recognize and manage the symptoms, in order to induce their prompt remission with substantial improvement of the patient's quality of life.

Taxane-induced nail toxicity is a treatable disease and if properly diagnosed and managed does not require treatment interruption or decrease of the dosage. For this reason, oncological patients should be advised to report any nail alterations during chemotherapy sessions and should be referred to a dermatological outpatient clinic as

soon as possible, in order to shorten the latency between the toxicity onset and the dermatological treatment. In Figure 4, we propose an algorithm for the correct management of patients with nail toxicity.

Statement of Ethics

The authors state that all subjects have given their informed consent and that the study protocol has been approved by the institute's committee on human research.

Disclosure Statement

The authors have no conflicts of interest to declare. There were no funding sources.

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