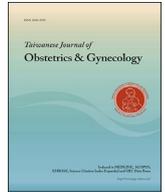




Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Case Report

Paclitaxel-related nail toxicity

Szu-Ting Yang^{a, b}, Min Cheng^{a, b}, Na-Rong Lee^{a, c}, Wen-Hsun Chang^{a, c}, Yi-Le Lee^{a, b}, Peng-Hui Wang^{a, b, d, e, *}^a Department of Obstetrics and Gynecology, Taipei Veterans General Hospital, Taipei, Taiwan^b Department of Obstetrics and Gynecology, National Yang-Ming University, Taipei, Taiwan^c Department of Nursing, Taipei Veterans General Hospital, Taipei, Taiwan^d Institute of Clinical Medicine, National Yang-Ming University, Taipei, Taiwan^e Department of Medical Research, China Medical University Hospital, Taichung, Taiwan

ARTICLE INFO

Article history:

Accepted 21 February 2019

Keywords:

Dermatological problems
Dose-dense chemotherapy
Nail
Paclitaxel

ABSTRACT

Objective: Nail change after chemotherapy is relatively unfamiliar with gynecological oncologist. It often occurs after docetaxel treatment. For gynecological tract cancers, paclitaxel might be most frequently used but nail change after paclitaxel treatment is seldom reported before.**Case report:** Two patients treated with the postoperative dose-dense weekly schedule of paclitaxel 80 mg/m² plus cisplatin 20 mg/m² every three weeks were complicated with nail problems during the treatment. They included onycholysis, subungual hemorrhage, proximal white subungual collections of pus obscuring the lunula (onychophosis), dystrophy, Beau's lines, pigmentation, and melanonychia. Topical use of anti-fungal cream and oral antibiotics stopped the nail disease progression and both patients had completed their chemotherapy without interruption.**Conclusion:** Clinicians should be aware of paclitaxel-induced nail toxicities. Adequate information, detailed preventive intervention, and early use of prophylactic and/or therapeutic agents to minimize the occurrence of severe morbidity, such as cellulitis and subsequent sepsis is important for women who need the continuous dose-dense paclitaxel chemotherapy.© 2019 Taiwan Association of Obstetrics & Gynecology. Publishing services by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

The standard therapy for women with advanced epithelial ovarian cancer (EOC), fallopian tube cancer (FTC) and primary peritoneal serous carcinomas (PPSC) includes the combination of the surgery and multi-agent chemotherapy (neoadjuvant or adjuvant) with/without targeted agents or anti-angiogenesis agents [1–3]. Although many patients with the above disease often received a combination of chemotherapy (paclitaxel 175 mg/m² and carboplatin dose equivalent to an area under the curve [AUC] 6 or cisplatin 75 mg/m²) every 3 weeks, results of the Japanese Gynecologic Oncology Group study number 3016 (JGOG 3016)-a dose-dense weekly schedule of paclitaxel 80 mg/m² plus carboplatin AUC 6 every 3 weeks showed a better progressive-free and overall

survival [4–7]. Taxanes, especially paclitaxel, are the main component of the front-line chemotherapy, recommended by NCCN guideline [8]. However, paclitaxel may produce several common and serious adverse events. Dermatological adverse events have been reported before, and especially chemotherapy-induced alopecia and prevalence might be up to 89% of patients [9]. Nail changes after paclitaxel treatment, although occurrence might be high and up to one-third to half of patients, are often neglected and unfamiliar to the majority of the gynecological oncologists. The following two cases showed the typical nail changes after a dose-dense weekly paclitaxel treatment.

Case presentation

Case 1

A 47-year-old woman with double cancers of ovarian seromucinous carcinoma, the International Federation of Gynecology and Obstetrics (FIGO) stage IIIC and endometrial adenocarcinoma, endometrioid type, grade 2, FIGO stage IIIA, was treated with a

* Corresponding author. Department of Obstetrics and Gynecology, Taipei Veterans General Hospital, National Yang-Ming University, 201 Section 2, Shih-Pai Road, Taipei, 11217, Taiwan. Fax: +886 255702788.

E-mail addresses: phwang@vghtpe.gov.tw, pongpongwang@gmail.com (P.-H. Wang).

modified JGOG 3016 regimen, including cisplatin 20 mg/m² every 3 weeks plus paclitaxel 80 mg/m² weekly after optimal debulking surgery. During the fourth cycle, she developed a subungual hemorrhage and onycholysis of fingernails and toes (Fig. 1). Antifungal cream was applied. The patient continued to receive chemotherapy without further complications.

Case 2

A 43-year-old woman with ovarian clear cell carcinoma, FIGO stage IC2 was treated with a modified JGOG 3016 regimen, cisplatin 20 mg/m² every 3 weeks plus paclitaxel 80 mg/m² weekly after complete staging surgery. During the fifth cycle, she developed a subungual hemorrhage of fingernails and toes, and melanonychia of fifth toe of right foot (Fig. 2). Antifungal cream was used. However, she had the pinched change on the fourth finger of right hand. Purulent discharge between the nail bed and nail matrix (onychophosis) with painful sensation occurred (Fig. 3). Oral antibiotic with clindamycin was prescribed, then the symptom was significantly improved. She continued chemotherapy without interruption.

Discussion

Taxanes, paclitaxel (Taxol®) and docetaxel (Taxotere®), serve as antineoplastic agents with wide broad antitumor activity have proved to be effective in the treatment of a variety of cancers [10]. The incidence of nail changes related to paclitaxel and docetaxel



Fig. 3. Purulent discharge (circle).

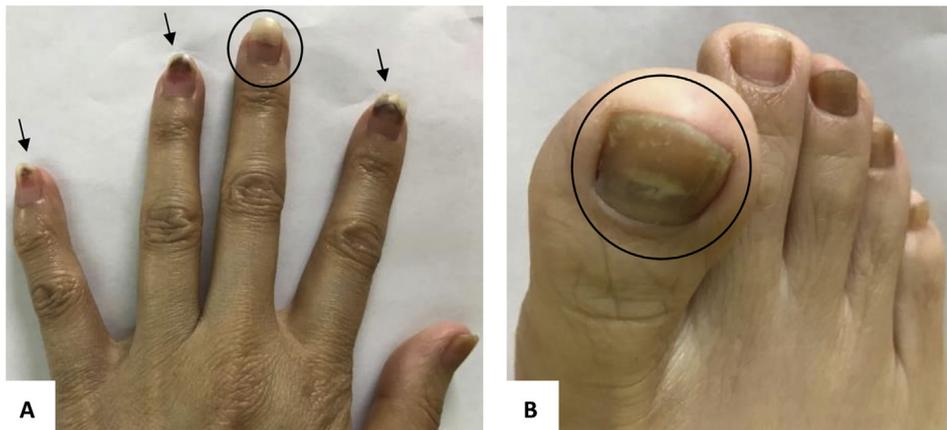


Fig. 1. (A) Subungual hemorrhage (arrow) and onycholysis (circle) and (B) proximal white subungual collections of pus obscuring the lunula (onychophosis) (circle).

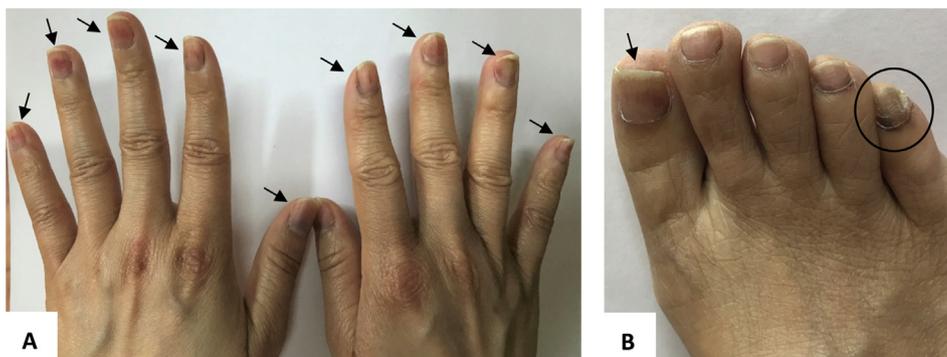


Fig. 2. (A) Subungual hemorrhage (arrow) and (B) subungual hemorrhage (arrow) and melanonychia (circle).

have been reported from 0 to 44% of in previous studies [11]. A meta-analysis reported that overall incidence of nail changes was 34.9% in patients receiving docetaxel, and 43.7% in patients receiving paclitaxel [12]. However, there are few reports describing paclitaxel-induced nail changes [11,12].

Nail changes, including onycholysis, subungual hemorrhage, proximal white subungual collections of pus obscuring the lunula (onychophosis), dystrophy, Beau's lines, pigmentation, and melanonychia, have been reported with paclitaxel [11,13–16], which also appeared in both patients we reported. The possible mechanisms of paclitaxel-induced nail changes include (1) onycholysis is separation nail matrix from the nail bed, which may develop due to direct damage to the nail matrix epithelium, composed of rapid regeneration cells; (2) onycholysis can lead to subungual hyperkeratosis; (3) Beau's lines can appear when the nail matrix is temporarily injured and arrest of growth; (4) nail plate pigmentation and melanonychia may occur through melanocyte activation and photosensitization; (5) subungual hemorrhage may be related to thrombocytopenia and vascular abnormalities [9–11,15–18].

These nail changes can further lead to cosmetic distress or severe infection. Managements include avoid trauma and contact irritants to the nails. Antifungal cream can be applied as prophylactic agent to infection. If severe onycholysis or pus formation occurred, it may be necessary to remove the nail plate. Antibiotics should be used in condition of nail infection. Coverage of antibiotic should include methicillin-susceptible *Staphylococcus aureus* (MSSA) as it is the most commonly an isolated pathogen [10,19]. In some severe cases, surgical intervention may be required. After discontinuation of chemotherapy, the nails will grow normally eventually in most patients.

The incidence of nail changes is related to the number of chemotherapy cycles and the intervals of paclitaxel administration. The incidence of nail change is related to an increasing cycle of chemotherapy. Comparing weekly regimen with every-3-week regimen of paclitaxel, hematologic toxicities are less, but nail changes are much more common with weekly regimen [10,11], and the nail changes from the patients we reported seemed to support this hypothesis. The limitation of our report is that we did not provide the incidence of nail changes in patients who underwent dose-dense paclitaxel regimen.

Conclusion

Clinicians should be aware of paclitaxel-induced nail toxicities, especially those patients who underwent a dose-dense weekly paclitaxel regimen. Patients experience this side effect as a problem impairing their quality of life. Every physician should provide adequate information to the patients about this phenomenon, and minimize the risk of occurrence of severe morbidity, which might impair the continuous chemotherapy and subsequently result in failure of therapy.

Conflict of interest

The authors declare that they have no competing interest.

Acknowledgements

This work was supported by grants from the Taipei Veterans General Hospital (V108C-085) and from the Ministry of Science and Technology, Executive Yuan (MOST: 106-2314-B-075-061-MY3), Taipei, Taiwan.

References

- [1] Kusunoki S, Terao Y, Hirayama T, Fujino K, Ujihira T, Ota T, et al. Safety and efficacy of neoadjuvant chemotherapy with bevacizumab in advanced-stage peritoneal/ovarian cancer patients. *Taiwan J Obstet Gynecol* 2018;57:650–3.
- [2] Wang PH. Neoadjuvant chemotherapy before definite operative approach for women with advanced-stage epithelial ovarian cancer. *Taiwan J Obstet Gynecol* 2018;57:623–4.
- [3] Sung PL, Wen KC, Horng HC, Chang CM, Chen YJ, Lee WL, et al. The role of α 2,3-linked sialylation on clear cell type epithelial ovarian cancer. *Taiwan J Obstet Gynecol* 2018;57:255–63.
- [4] Katsumata N, Yasuda M, Isonishi S, Takahashi F, Michimae H, Kimura E, et al. Long-term results of dose-dense paclitaxel and carboplatin versus conventional paclitaxel and carboplatin for treatment of advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer (JGOG 3016): a randomised, controlled, open-label trial. *Lancet Oncol* 2013;14:1020–6.
- [5] Chan JK, Brady MF, Penson RT, Huang H, Birrer MJ, Walker JL, et al. Weekly vs. every-3-week paclitaxel and carboplatin for ovarian cancer. *N Engl J Med* 2016;374:738–48.
- [6] McGuire WP, Hoskins WJ, Brady MF, Kucera PR, Partridge EE, Look KY, et al. Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and IV ovarian cancer. *N Engl J Med* 1996;334:1–6.
- [7] Piccart MJ, Bertelsen K, James K, Cassidy J, Mangioni C, Simonsen E, et al. Randomized intergroup trial of cisplatin-paclitaxel versus cisplatin-cyclophosphamide in women with advanced epithelial ovarian cancer: three-year results. *J Natl Cancer Inst* 2000;92:699–708.
- [8] Stasenko M, Reynolds RK, Johnston C, Brackman M, McLean K, Uppal S. Adherence to hematologic hold parameters in carboplatin and dose-dense paclitaxel chemotherapy for ovarian malignancies: a survey of NCCN member institutions. *J Natl Compr Cancer Netw* 2016;14:849–53.
- [9] Marks DH, Qureshi A, Friedman A. Evaluation of prevention interventions for taxane-induced dermatologic adverse events: a systematic review. *JAMA Dermatol* 2018;154:1465–72.
- [10] Sibaud V, Leboeuf NR, Roche H, Belum VR, Gladieff L, Deslandres M, et al. Dermatological adverse events with taxane chemotherapy. *Eur J Dermatol* 2016;26:427–43.
- [11] Minisini AM, Tosti A, Sobrero AF, Mansutti M, Piraccini BM, Sacco C, et al. Taxane-induced nail changes: incidence, clinical presentation and outcome. *Ann Oncol* 2003;14:333–7.
- [12] Capriotti K, Capriotti JA, Lessin S, Wu S, Goldfarb S, Belum VR, et al. The risk of nail changes with taxane chemotherapy: a systematic review of the literature and meta-analysis. *Br J Dermatol* 2015;173:842–5.
- [13] Luftner D, Flath B, Akivakis C, Schweigert M, Prinz B, Mergenthaler HG, et al. Dose-intensified weekly paclitaxel induces multiple nail disorders. *Ann Oncol* 1998;9:1139–40.
- [14] Flory SM, Solimando Jr DA, Webster GF, Dunton CJ, Neufeld JM, Haffey MB. Onycholysis associated with weekly administration of paclitaxel. *Ann Pharma* 1999;33:584–6.
- [15] Ghetti E, Piraccini BM, Tosti A. Onycholysis and subungual haemorrhages secondary to systemic chemotherapy (paclitaxel). *J Eur Acad Dermatol Venereol* 2003;17:459–60.
- [16] Garshick MK, Myskowski P, Scher R. Paclitaxel-associated melanonychia. *Cutis* 2015;95:E12–4.
- [17] Ohn J, Choe YS, Park J, Mun JH. Dermoscopic patterns of fungal melanonychia: a comparative study with other causes of melanonychia. *J Am Acad Dermatol* 2017;76:488–93. e2.
- [18] Nevares-Pomales OW, Sarriera-Lazaro CJ, Barrera-Llaurador J, Santiago-Vazquez M, Lugo-Fagundo N, Sanchez JE, et al. Pigmented lesions of the nail unit. *Am J Dermatopathol* 2018;40:793–804.
- [19] Virgen CA, Belum VR, Kamboj M, Goldfarb SB, Blinder VS, Gucaip A, et al. The microbial flora of taxane therapy-associated nail disease in cancer patients. *J Am Acad Dermatol* 2018;78:607–9.