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Photosensitive Rash in Association with Porphyrin Biosynthesis Possibly Induced by Docetaxel and Trastuzumab Therapy in a Patient with Metastatic Breast Carcinoma

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Docetaxel (Taxotere), an anticancer agent, is known to cause various reactions, including hypersensitivity, oedema, skin toxicity with erythrodysesthesia syndrome, infusion site reactions, alopecia, nail onycholysis, nail pigmentation, photosensitivity, scleroderma and stomatitis. However, of all the reported effects, photosensitivity has only rarely been described in the literature. We experienced a case of cutaneous photosensitivity with aberrations in porphyrin biosynthesis that developed 1 month after the patient received combination chemotherapy consisting of docetaxel and trastuzumab. The eruption resolved with sun avoidance and discontinuation of docetaxel therapy. To our knowledge, this is the first case of a photosensitive reaction with enhanced levels of porphyrins during docetaxel therapy.

Key words: porphyria – trastuzumab – docetaxel – photosensitive reactions

INTRODUCTION

Combination therapy with trastuzumab and docetaxel is used for the treatment of metastatic breast cancer. Trastuzumab is a recombinant DNA-derived humanized monoclonal immunoglobulin G1 kappa antibody that binds to the extracellular domain of the human epidermal growth factor receptor 2 (HER2) receptor (1). It has an antiproliferative effect on tumour cells that overexpress HER2. Cutaneous side effects due to trastuzumab are rarely observed. Docetaxel is a member of the taxane class of chemotherapeutic agents. It binds to free tubulin and stabilizes microtubule activity, which results in the inhibition of mitosis (1). Although a majority of patients receiving docetaxel experience some degree of cutaneous reaction, the eruptions are usually mildly symptomatic and almost always self-limiting (2–4). These reactions include hypersensitivity, oedema, erythrodysesthesia syndrome, erythema multiforme major, alopecia, nail changes, photosensitivity, scleroderma and subacute cutaneous lupus erythematosus (SCLE) (1–5). Here, we report a photosensitive reaction with enhanced levels of porphyrins in a case of metastatic breast cancer during combination chemotherapy with trastuzumab and docetaxel that resolved after discontinuation of docetaxel.

CASE REPORT

A 63-year-old woman was treated with docetaxel and trastuzumab for metastatic breast cancer. She received trastuzumab 8 mg/kg as a loading dose followed by 6 mg/kg in combination with docetaxel 75 mg/m^2, both given every 3 weeks as a 1 h infusion. After the second cycle of therapy, she presented with asymptomatic erythematous patches on her hands and face, widespread papules and pustules on her scalp after sun exposure (Figs 1 and 2). Histopathology of an incisional biopsy specimen showed perivascular lymphocytic infiltration in the papillary dermis. Examination of urinary porphyrins showed increased levels of uroporphyrin (50.9 μg/day), pentacarboxyporphyrin (7 μg/day), coproporphyrin I (58.7 μg/day), coproporphyrin III (175.9 μg/day) and total porphyrins (298 μg/day). δ-Aminolevulinic acid and porphobilinogen levels were normal. Hepatitis virus titres were as follows: hepatitis B surface antigen, negative-0.25 S/CO; hepatitis C virus, negative-0.10 S/CO. Liver enzymes before and after chemotherapy were aspartate aminotransferase, 22/29 U/l; alanine aminotranferease, 28/35 U/l; and γ-glutamyl transpeptidase, 42/60 U/l. Anti-double-stranded DNA, anti-nuclear, anti-ro (SS-A), anti-la (SS-B), anti-histone and anti-smith antibodies were negative. C3 and C4 were within normal ranges. The

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Figure 1. Widespread papules and pustules on the scalp. A colour version of this figure is available as supplementary data at http://www.jjco.oxfordjournals.org.



Figure 2. Mild erythema on the nose, perioral and malar areas. A colour version of this figure is available as supplementary data at http://www.jjco.oxfordjournals.org.

patient avoided solar radiation. Docetaxel was withdrawn and trastuzumab was continued. One month after cessation of docetaxel therapy, urinary porphyrin levels returned to normal ranges. The eruption resolved with no pigmentation.

DISCUSSION

Clinical investigations of docetaxel as a single agent or in combination with other chemotherapy drugs demonstrate favourable anti-tumour activity in a range of solid tumour types. The most important and severe side effect of docetaxel is dose-dependent neutropenia. An early Phase 1 study of docetaxel reported skin toxicity in 12 patients, with 70% experiencing some degree of skin reaction (3). In a more recent Phase 2 study of docetaxel (35 mg/m^2/weekly) in patients with anthracycline-pretreated metastatic breast cancer, the incidence of Grade 3 cutaneous toxicity was 19% (4). Common cutaneous side effects include discrete erythematous to violaceous patches, as well as oedematous plaques similar to acral erythema, or fixed-plaque erythrodysesthesia (3). The other reported skin manifestations are as follows: hypersensitivity reactions; erythema multiforme; alopecia; nail changes such as pigmentation, onycholysis, paronychia, scleroderma, SCLE, flagellata erythema and supravenous discoloration; and radiation recall dermatitis (1–5). The aetiology of skin manifestations following treatment with docetaxel remains unknown. These may be direct toxic effects of docetaxel or the vehicle of the drug, called polysorbate 80.

Drug-induced photosensitivity refers to the development of cutaneous disease as a result of the combined effects of a chemical and light. When photoactivation of the chemical occurs, one or more cutaneous manifestations may arise. Drug-induced photosensitivity reactions may result in phototoxicity, photoallergy, lichenoid reactions, pseudoporphyria or SCLE. Pseudoporphyria is characterized by a bullous reaction that clinically and histologically resembles porphyria cutanea tarda (PCT). However, no demonstrable porphyrin abnormalities are present. The histological features of pseudoporphyria are similar to those of PCT with subepidermal bullae and festooning of the dermal papillae. In the present case, the onset of cutaneous photosensitivity with aberrations in porphyrin biosynthesis developed 1 month after the patient underwent combination chemotherapy consisting of docetaxel and trastuzumab. The eruption resolved with sun avoidance and discontinuation of docetaxel therapy. Cessation of docetaxel resulted in a prompt decline in urinary porphyrins, which suggests that porphyrins play a causative role. Thus, it seems that the main trigger for the reaction was docetaxel. Furthermore, the cutaneous side effects of trastuzumab are very rare when compared with those of docetaxel therapy. A porphyrinogenic effect of paclitaxel was also observed in tissue cultures of primary neural cells, which could explain the aberrations in porphyrin biosynthesis observed here (1). In the literature, only one case has been described that involved eruptions resembling cutaneous porphyria during the administration of paclitaxel and trastuzumab for metastatic breast cancer (1). The authors suggested that the main trigger for the reaction was either paclitaxel or the combined interaction of paclitaxel and trastuzumab, which increased the likelihood of a cutaneous drug reaction (1). In our case, however, the eruption and histopathology were not those characteristic of porphyria. Moreover, the localization of the lesions on sun-exposed areas and concurrent elevation of urinary

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porphyrin levels suggested a photosensitive rash that affected porphyrin biosynthesis. Here, docetaxel may have elicited a mild form of dermatitis. The dermatitis seen with docetaxel may have resulted from skin photosensitivity that induced a mild form of chemical porphyria. In patients who develop drug-induced dermatitis, an inherited predisposition to porphyria may play a role. The mechanism by which docetaxel may have revealed PCT remains elusive and could possibly have involved decreased uroporphyrinogen decarboxylase activity in the liver or potentiation of the phototoxic effects of porphyrin, which would contribute to the cutaneous toxicity of docetaxel. The accumulation of similar reports in the future will elucidate the real aetiology.

In conclusion, treatment with docetaxel followed by sun exposure may cause photosensitive reactions that affect porphyrin biosynthesis. When prescribing docetaxel to patients, healthcare professionals need to be aware of the drug's potential side effects and the appropriate strategies for preventing unnecessary patient suffering.

Conflict of interest statement

None declared.

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