

A rare cutaneous phototoxic rash after vandetanib therapy in a patient with thyroid cancer

A case report

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Abstract

Rationale: Vandetanib is effective for treating symptomatic or progressive medullary thyroid cancer (MTC) in patients with unresectable locally advanced or metastatic disease, but its toxicity such as photosensitivity reactions should be considered. It is a rare adverse effect of this drug but might cause severe morbidity and even mortality.

Patient concerns: A 26-year man with MTC developed phototoxic rashes on the sun-exposed areas of his shin after 15 days from the initiation of vandetanib treatment. Grade II skin toxicity was evaluated based on the Common Terminology Criteria for Adverse Events standard.

Diagnoses: Drug-induced phototoxic rash.

Interventions: The vandetanib dose was reduced by 30%, and the application of topical steroids and sunscreen was adopted.

Outcomes: After dose reduction of vandetanib, the symptoms of vandetanib-induced phototoxic rash resolved, although residual pigmentation was observed.

Lessons: Close attention should be paid to the adverse effect of vandetanib, phototoxic rash, and patients should be advised on the prevention and treatment measures.

Abbreviations: CTCAE = common terminology criteria for adverse events, EGFR = epidermal growth factor receptor, MTC = medullary thyroid cancer, RET = rearranged during transfection, VEGFR = vascular endothelial growth factor receptor.

Keywords: cutaneous phototoxic rash, medullary thyroid cancer, pharmaceutical care, vandetanib

1. Introduction

Vandetanib is an oral chemotherapeutic agent that targets multiple kinases, such as vascular endothelial growth factor receptor (VEGFR), RET, and epidermal growth factor receptor (EGFR).^[1] A global randomized phase III clinical trial demonstrated the

efficacy of vandetanib compared to that of placebo in terms of prolongation of overall survival in patients with symptomatic or progressive unresectable, locally advanced or metastatic medullary thyroid cancer (MTC).^[2,3] Furthermore, vandetanib is now used not only in MTC patients but also in patients with advanced non-small cell lung cancer (NSCLC) characterized by RET rearrangement^[4-6] and hepatocellular carcinoma (HCC) patients who have previously received treatment.^[7]

The common adverse drug reactions of vandetanib (>20%) are diarrhea/colitis, rash, acneiform dermatitis, hypertension, nausea, headache, fatigue, anorexia, abdominal pain, hypocalcemia, hypoglycemia, and increased alanine aminotransferase (ALT). Importantly, clinical trials of MTC and lung cancer showed that 28% to 71% of patients treated with vandetanib developed skin reactions, including rash, acneiform dermatitis, skin dryness, pruritus, photosensitivity reactions, and hand-foot skin reaction (HFSR). Of these, 3% to 6% of patients showed severe skin reactions (grade, ≥ 3).^[8-13] Lichenoid eruptions on the sun-exposed areas of the shin and subacute cutaneous lupus erythematosus have been reported in patients treated with vandetanib.^[14] Additionally, severe, and in some cases fatal, skin reactions, including Stevens-Johnson syndrome, have been reported following vandetanib use.^[15,16] Thus, vandetanib-treated patients should be counseled to use sunscreen and wear protective clothing when stepping into sunlight. To date, the underlying mechanism of photosensitivity reactions caused by vandetanib remains unclear. Herein, we describe a case of a patient with MTC who developed photosensitivity reactions after treatment with vandetanib.

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2. Case presentation

The patient was a 26-year-old man who was admitted to our hospital because of goiter and enlargement of lymph nodes in the neck for 7 months; he was diagnosed with MTC along with lymph node metastasis. There was no family history of MTC or skin system disease. PET-CT performed on August 23, 2017, showed multiple bilateral enlarged lymph nodes in the neck, left subclavian fossa, and right upper mediastinum and very low-density nodules in the left inferior lobe of the thyroid, which were considered as malignant lesions. Ultrasonography of the neck conducted on August 28, 2017, showed hypoechoic nodules in the left lobe of the thyroid, 2.6×1.3 cm in size with an unclear boundary, an irregular shape, multiple strong echoes, and abundant blood flow. Multiple hypoechoic enlarged lymph nodes were fused in the left side of the neck, with the maximum being 5.3×3.3 cm, whereas the maximum size of the nodes in the right neck was 2.4×2.1 cm. Hypoechoic nodules 1.2×0.8 cm in size were noted in the VI area of the left neck. Multiple hypoechoic nodules were seen around the trachea, which was fused with each other, with the maximum size being 2.8×1.8 cm. On September 5, 2017, endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) cell smear of thyroid nodules indicated possible MTC. On October 2017, calcitonin level was found to be more than 2000 pg/mL and carcinoembryonic antigen level was found to be 92.84 ng/mL.

On September 26, 2017, vandetanib (300 mg, qd) was administered orally. Fifteen days later, the patient developed a rash, pinpoint to millimeter-sized papules and blisters on the face, neck, and back. The skin lesions were dense, practically fused into sheets, and caused mild pain. No special treatment was provided, and only the lotion was applied on the rash.

The scattered rashes on the back were considered to be the characteristic of the skin toxicity of EGFR antagonists and were usually dose-dependent (Fig. 1). After 2 months, the rash on the



Figure 1. Rashes dispersed on the back similar in appearance to millet grains.



Figure 2. Face and neck showing rashes, sparing areas not exposed to the sun.

face and neck worsened, with ecchymosis, scaling, and itching. Most of the lesions were concentrated in the sun-exposed areas, and a few were scattered along the edge of the non-exposed areas. The boundaries were clear (Figs. 2 and 3). Three months later, the edema on the face and neck cleared and residual melanin deposition was observed (Figs. 4 and 5).

This patient had a clear medication history. The rash first developed in the predominantly sun-exposed areas, and the boundary between the exposed and non-exposed areas was clear. Therefore, a diagnosis of phototoxic rashes was performed. According to the Common Terminology Criteria for Adverse Events (CTCAE4.03), the patient was classified as showing grade II skin toxicity. Local symptomatic treatments such as a steroid



Figure 3. The back of the hand.



Figure 4. Desquamation, edema, and melanosis on the face and the neck.

ointment and moisturizer were used. Based on previous literature, the vandetanib dose was reduced to 200 mg daily. After follow-up outside the hospital, it was found that the patient took vandetanib (200 mg, qd) on time; the rash had not worsened further, and the patient had good tolerance. The phototoxic rash resolved within 1 month after vandetanib dose reduction. In

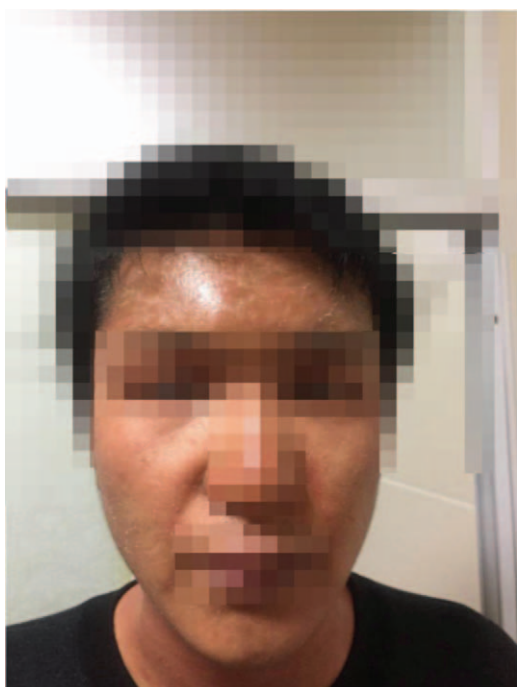


Figure 5. Desquamation, edema, and melanosis on the forehead and face.

March 2018, the patient underwent total thyroidectomy after which levothyroxine sodium tablets (100 µg, qd) and vandetanib were orally administered. Despite continuing vandetanib administration at the reduced dose, the phototoxic rash did not reappear.

3. Discussion

Vandetanib, an oral chemotherapeutic agent targeting multiple kinases, such as VEGFR, EGFR, and RET, partially inhibits a variety of kinases at nanomolar concentrations and usually affects multiple signaling pathways that stimulate tumor proliferation, angiogenesis, and tumor invasion and metastasis. More than 300 patients with unresectable, locally advanced or metastatic, sporadic or inherited MTC were enrolled in an international phase III randomized trial of vandetanib therapy (300 mg/d). After a median follow-up of 24 months, the progression-free survival (PFS) of the patients randomly assigned to the vandetanib group was significantly greater than in the patients in the placebo group (HR: 0.46, 95% CI: 0.31–0.69).^[13,18] Although the median PFS was not achieved in the vandetanib group, it was estimated to be 30.5 months, compared to 19.3 months in the placebo group. Furthermore, the objective remission rate (ORR) in the vandetanib group was significantly higher than that in the placebo group (45% vs 13%).

Unlike traditional cytotoxic drugs, vandetanib can inhibit not only EGFR but also VEGFR-2 and VEGFR-3. Furthermore, the adverse effects of vandetanib are more closely associated with VEGF. For example, the level of creatine kinase-MB (CK-MB), a cardiac enzyme, was increased to near the upper limit of the normal value after a few days of vandetanib treatment and hypoglycemia-like weakness developed after meals. Furthermore, patients reported fatigue after 3 weeks of vandetanib therapy as well as slight elevations in blood pressure. A few patients showed severe phototoxic skin rashes, which are a common adverse effect of VEGF inhibitor drugs. Many drugs, especially EGFR inhibitors that interfere with signal transduction and multi-target small-molecule tyrosine kinase inhibitors, can cause significant skin complications, which sometimes could be dose-limiting.^[19] In a meta-analysis of dermal toxicity, the incidence of skin rashes due to vandetanib was the highest (41%). A positive correlation has been reported between skin toxicity and improvement in prognosis after sunitinib and sorafenib treatments. Whether the skin toxicity caused by vandetanib is related to the survival time needs further study.^[20]

Cutaneous photosensitive reactions are by far the most common drug-induced phototoxic skin rashes; they are caused by the release of energy and cell damage after the pathogenic drugs absorb ultraviolet light. The most common correlation is with ultraviolet A light (UVA), although ultraviolet B light (UVB) and visible light can also trigger related reactions when some drugs are used. The exact mechanism of vandetanib-induced cutaneous photosensitive diseases remains unclear. An *in vitro* study showed that vandetanib has a low-molecular-weight polycyclic protein structure similar to that of other known photosensitizers, and can exert its photosensitive effect by inducing active oxygen, DNA dissociation, and cell apoptosis. Studies have also shown that vandetanib inhibits the ABCG2 transporter-associated protein, which is a porphyrin-related mechanism.^[21]

Drug-induced photosensitization is usually divided into phototoxic reactions and photoallergy. The clinical character-

istics and pathogenic substances of these two reactions are different; most drug-induced photosensitization is caused by phototoxic reactions. A phototoxic reaction is characterized by excessive sunburn, which progresses within minutes to hours of exposure and is limited to the exposed skin.^[22] Patients with severe exposure may develop blisters or bullae.^[23] The results of the skin biopsy showed that keratinocyte vacuolization and apoptosis are similar to those associated with ordinary sunburn.^[24] Chang et al^[17] reported thyroid cancer in a patient whose work involved frequent exposure to sunlight; the patient developed phototoxic rashes on the head, chest, and feet after treatment with vandetanib (300 mg, qd). It is a rare adverse effect of this drug but might cause severe morbidity and even mortality. In the present case, cutaneous photosensitive reactions were observed. Although our patient did not undergo phototesting and/or photo patch testing, rashes symmetrically developed in the “V” shaped area of the face, ears, neck, and chest. The relatively shaded areas of the upper lip, lower chin and neck, upper eyelid, nasolabial groove, and posterior auricle were not involved; these characteristics are similar to those of phototoxic skin rash, indicating that the adverse reaction in this patient was phototoxic reactive rash.

Treatment of cutaneous photosensitivity diseases, whether they are characterized by phototoxic reactions or photoallergy, should as far as possible, including stoppage of the use of pathogenic drugs or chemicals that can cause exogenous photosensitive reactions. Furthermore, measures to protect oneself from the sunlight are essential, such as avoiding sun exposure, wearing sun-protective clothing, and using sunscreens. Photosensitive reactions induced by exogenous substances are usually the most serious. It is necessary to use a broad-spectrum light-screening agent that can fully protect against UVA. For most phototoxic reactions, a cold or wet compress, calamine lotion, or aloe-based gel can relieve pain and discomfort. Mild emollients, such as liquid paraffin/soft paraffin 50/50 can be used for intact skin depending on the patient's tolerance. Fractured blisters should be gently cleaned with mild soap and water and then covered with a wet dressing, such as saline or vaseline-soaked gauze. Topical anesthetics may cause contact allergy; therefore, they should be avoided. For the treatment of cutaneous pain and inflammation, oral non-steroidal anti-inflammatory (NSAIDs) drugs were recommended. The recommended dose of ibuprofen is 400 to 800 mg to be taken orally 3 to 4 times daily for adults and children over the age of 12 years. For children aged 6 months to 12 years, ibuprofen should be administered at 4 to 10 mg/kg every 6 to 8 hours. The first symptoms should be treated as soon as they become obvious, and the treatment should be continued for 24 to 48 hours. It should be noted, however, that there are no clear treatment recommendations to guide the safety of repeat chemotherapy for patients with severe photosensitization caused by vandetanib. It has been reported that patients with NSCLC developed cutaneous photosensitivity diseases after receiving vandetanib, and skin adverse effects were alleviated 1 month after vandetanib withdrawal. Docetaxel plus cisplatin chemotherapy regime was administered to manage tumor progression, which led to the recurrence of cutaneous photosensitivity diseases. Cutaneous photosensitivity diseases caused by docetaxel are rare, and there have been no reports about interactions between docetaxel and vandetanib.^[25]

Prevention of phototoxic rashes is particularly important during the use of a drug that can cause phototoxic rashes when it is not appropriate to adjust the medication regimen. First, midday

sun exposure (10:00 to 16:00 hours) should be avoided and protective clothing (such as long-sleeved shirts and trousers) should be used. Window stickers for blocking UVR can be installed on cars. Broad-spectrum sunscreens that protect against both UVA and UVB are recommended for use as well.

4. Conclusion

In our patient with MTC, cutaneous photosensitivity diseases developed after treatment with vandetanib and the rashes resolved after treatment with a steroid topical ointment and dose adjustment. Thus, measures for complete protection from sun should be undertaken during the administration of vandetanib, and pharmacists recommend that a detailed history of photosensitization and a comprehensive skin examination are essential for an accurate diagnosis of phototoxic or photoallergic reactions. If the diagnosis is still unclear, a light test and/or patch test will be helpful. In addition, it should be noted that patients must stop using glucocorticoids as well as other systemic immunosuppressive agents for at least 2 weeks and antihistamines for at least 1 or 2 days before the light test.^[26] Topical medications (such as topical corticosteroids) should also be discontinued for 1 to 2 weeks. In the case of inappropriate adjustment of medication, patients should be fully informed of the prevention and treatment of phototoxic reactive rashes.

Author contributions

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Methodology: Hua Yan Zhang.

Resources: Bin Zhang.

Writing – original draft: Yue Yin.

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