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Pazopanib Induced Hand-Foot Syndrome in a Patient Previously Treated with Sunitinib: A Possible Cumulative Skin Toxicity?

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Abstract

Hand-foot syndrome (HFS), also known as palmar-plantar erythrodysesthesia, is a skin toxicity that could be observed during target therapies such as with tyrosine-kinase inhibitors (TKI). It usually develops within the first 2 - 4 weeks of drug administration. We present a case of HFS induced by Pazopanib after 2 months of treatment, in patients previously treated with Sunitinib, suggesting a possible cumulative toxicity of two drugs. The clinical and therapeutic management of skin adverse reactions during TKI therapy usually requires 25% dose reduction and adequate local treatment. It is important for the clinicians to recognize clinical signs and symptoms of such skin toxicities. Attention should be paid especially when two or more drugs from the same class are used in combined treatment.

Keywords

Hand-Foot Syndrome, Pazopanib, Sunitinib, Tyrosine-Kinase Inhibitors, Cumulative Toxicity

1. Introduction

Sunitinib and Pazopanib are the most prescribed targeted therapies for the systemic management of advanced renal cell carcinoma (RCC). Sunitinib is employed in first-line treatment of RCC [1]. Since members of the cdk and cyclin family were reduced in parallel, modifications of the cdk-cyclin axis (particularly cdk1-cyclin B and cdk2-cyclin A) may be one mechanism by which Sunitinib exerts its antitumour effect. Sunitinib up-regulated also p19 and p27, directly associated with advanced disease and reduced cancer specific survival in RCC cells [2]

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[3]. Pazopanib is second-generation potent inhibitor of multiple protein targets involved in tumor cell proliferation and angiogenesis. In this process, several proangiogenic factors are involved, with a central role for the vascular endothelial growth factor (VEGF) family. Inhibition of this pathway has demonstrated antitumor activity in several tumor types, including renal cell carcinoma [4]. Pazopanib inhibits this signaling pathway via ATP-competitive inhibition of VEGFR-1, VEGFR-2, and VEGFR-3. Similar activity has been demonstrated against platelet-derived growth factor receptor (PDGFR)-α, PDGFR-β, fibroblast growth factor receptor (FGFR)-1, FGFR-3, and c-Kit [5]. Cutaneous adverse effects are among the most frequently observed toxicities with many targeted agents, and their intensity can be dose-limiting or lead to therapy discontinuation [6]. Hand-foot syndrome (HFS), also known as palmar-plantar erythrodysesthesia, is a frequently seen skin toxicity associated with chemotherapeutic agents like 5-fluorouracil, capecitabine and tyrosine-kinase inhibitors (TKI) like Sunitinib; less commonly with Pazopanib. Data from the literature are variable and indicate that 9% - 62% of studied patients receiving TKI develop HFS usually within the first 2 - 4 weeks of drug administration [7] [8]. We present a case of HFS induced by Pazopanib after 2 months treatment, in a patient previously treated with Sunitinib.

2. Case Report

A 52-year-old female patient was diagnosed as a case of left renal cell carcinoma (clear cell histology) in 2002. In 2014, metastasis were detected, she started treatment with TKI Sunitinib 50 mg daily. After 3 months of treatment, the patient complained of gastrointestinal problems, so Sunitinib was interrupted. Pazopanib 800 mg daily was started. After two months of treatment, the patient reported desquamation of the hands and soles. She was initially treated with topical urea 40% with temporary benefit. Six months later, because of the persistence of gastrointestinal symptoms and worsening of skin manifestations with painful, erythematous and hyperkeratotic lesions of palms and soles compatible with HFS of grade 2, the treatment with Pazopanib was reduced by 25% (**Figure 1**, **Figure 2**). Treatment with topical urea 40% cream, clobetasol 0.05% ointment and 2.5% lidocaine was prescribed. After 3 months, at the follow-up, the patient showed complete resolution of the plantar manifestations and only a slight residual hyperkeratosis of the sole. Furthermore, the renal cell carcinoma was under remission.

3. Discussion

Clinically, HFS presents as symmetric erythematous lesions on skin surfaces exposed to repeated pressure or friction (**Table 1**). All grades (1-3) and high-grade (grade 3) HFS reaction have been variably reported in 6% - 19% of patients treated with Sunitinib [8].

The pathogenesis of HFS is poorly understood. Although there is no consensus that different causative drugs share a single underlying mechanism, current evidence suggests an underlying direct toxic effect as the most likely cause. The predilection of HFS for the palms and soles may be due to the high concentration of eccrine

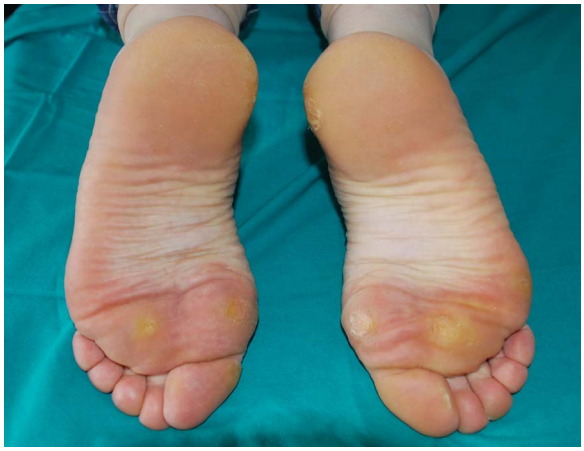

Figure 1. Erythematous and hyperkeratotic lesions of the soles.

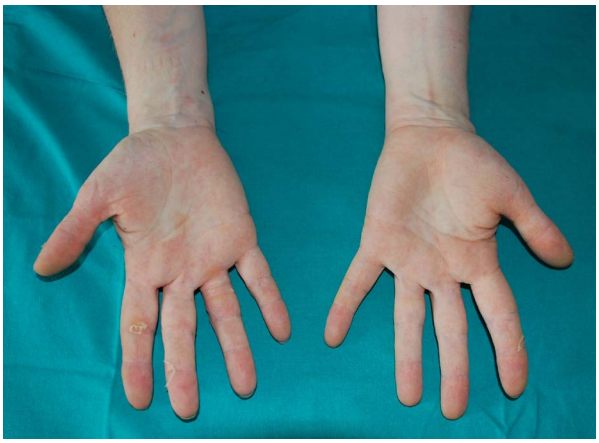

Figure 2. Erythema and desquamation of the palms.

Table 1. Clinical classification and management for all grade HFS.

Grade	Syptoms	Management
1	Minimal skin changes without pain	Emollients and keratolytics
2	Skin changes with pain limiting activities of daily living	+ Topical steroids (class I/II) and topical anesthetics, nonsteroidal anti-inflammatory drugs
3	Severe skin changes with debilitating pain limiting self-care	+ Antiseptic soaks; treatment interruption

ducts in these areas. It is possible that the tick stratum corneum of the palms and soles acts as a reservoir, as hypothesized for the doxorubicin-associated HFS [9]. Furthermore, capillary microtrauma at sites predisposed to mechanical and frictional stress, such as hands, feet, axillae, and intertriginous areas with consequent extravasation of the drug into surrounding tissue should be an explanation of HFS. The presence of target molecules as TKI may lead to major oxidative damage and local production of toxic free radicals and induce apoptosis of keratinocytes. There are very few studies reporting Pazopanib-induced HFS. However, the reported cases of HSF are generally described only for the single drug therapy, and the possible cumulative toxicity of these agents is not reported in the literature.

Although skin toxicity associated with Pazopanib is less reported than with Sunitinib [7] [8]. In our patient, who received both Sunitinib and Pazopanib, drug-induced reaction was temporary more related to the second one. It should be important to clarify, in these cases treated with both Sunitinib and Pazopanib, if the first one induced delayed adverse skin reaction or the second one, Pazopanib, plays a role in direct skin toxicity. Furthermore, we suggest that both drugs take part in the HFS induction probably due to cumulative skin toxicity.

It is possible that these toxicities could represent a delayed reaction or may arise with the introduction of a second drug from the same class.

The clinical and therapeutic management of skin adverse reactions during TKI therapy usually requires 25% dose reduction and adequate local treatment. It is important for the clinicians to recognize clinical signs and symptoms of such skin toxicities. Attention should be paid especially when two or more drugs from the same class are used in combined treatment or subsequently as in our case. There are no measures available used to prevent the Pazopanib and Sunitinib's cumulative toxicity so, more attention should be paid to cutaneous side effects or others such as gastrointestinal side effects and we are conscious that this is a single case of HFS but we suggest the clinicians to evaluate a possible cumulative toxicity of drugs with the same pharmacologic target.

4. Conclusion

Sunitinib and Pazopanib are among the most prescribed targeted therapies for the systemic management of advanced RCC but with only a partial response. At the moment several therapeutic agents showed promising pharmacodynamic effects and have been tested with success in preclinical models of RCC and are therefore awaiting clinical evaluation. Particularly, dual inhibitors of PGAM1 and 6-PGDH (e.g., PGMI-004A) and inhi-

bitors of the relatively cancer-specific target PFK-FB3 such as PFK15 warrant further investigation [10]. All grades HFS reactions have been variably reported in patients treated with Sunitinib and Pazopanib [8]. Hand-foot syndrome may represent a challenge regarding its causative agent but it is important to consider possible cumulative toxicities in cases of sequential administration of the drugs from the same class. Therefore, in our patients, HFS may be considered as possible cumulative skin toxicity induced by both Sunitinib and Pazopanib.

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