

Hypopigmentation of the Skin and Hair Associated with Targeted Therapies

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ABSTRACT

In the last two decades the US Food and Drug Administration has granted approval for multiple molecules for use in the treatment of cancer. These targeted therapies, aimed at inhibiting specific molecules, cause numerous adverse effects at the skin, for example, acneform dermatitis, mucosal, hair and nail alterations, and depigmentation of skin and hair, which have been seldom described in the literature. In this article we will focus on the side effects of tyrosine kinase inhibitors in particular and try to show how these drugs affect melanogenesis in hair follicles, triggering changes in skin and hair pigmentation. (J CANCEROL. 2014;1:67-72)

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In the last two decades the US Food and Drug Administration (FDA) has granted approval for multiple molecules for use in the treatment of cancer. Treatments are becoming increasingly specific and selective as a result of better understanding of the signaling pathways involved in certain cancers. Though there are generally fewer systemic side effects from these types of targeted treatments, they do cause toxic effects in skin, hair, nails, and mucous membranes. It is important to know about them to diagnose and treat patients. In many articles it is proposed that these adverse effects result from good antitumor response.

In this article we will focus on the side effects of tyrosine kinase inhibitors (TKI) in particular and try to show how these drugs affect melanogenesis in hair follicles, triggering changes in skin and hair pigmentation.

The pilosebaceous unit consists of the hair follicle, the sebaceous gland, and the hair erector muscle.

Melanoblasts can be detected at around 50 days of gestation and originate in the neural crest where several factors such as Pax3 and microphthalmia transcription factor activate expression of enzyme DOPAchrome tautomerase (tyrosinase-related protein-2, TRP-2) to stimulate melanin synthesis in early melanoblasts. The melanoblasts then migrate to the dermis and epidermis thanks to other signaling factors such as endothelin receptor type B and, primarily, receptor c-Kit (expressed in the proliferation of the melanocytes that synthesize melanin: outer root sheath and matrix), and during hair follicle placode formation, the melanoblasts proliferate and start to produce melanin together with growth of the hair fiber (through SCF/c-Kit)¹.

The KIT gene, which is located on the long arm of chromosome 4 at position 12 (4q12), plays a pivotal role in the step described above since it encodes a type III TK receptor for stem cell factor (SCF) from which melanocytes develop, proliferate, survive, and migrate in the skin².

The hair cycle has three phases: anagen, catagen, and telogen. Anagen is the growth phase and usually lasts 2-8 years; 80-90% of scalp hair is in this phase. The catagen phase is involutonal stage, during which the lower portion of the hair follicle undergoes apoptosis and lasts for 3-4 weeks; and the telogen phase is a resting stage, which lasts 3-4 months; then the hair falls out and the cycle starts all over again.

Hair follicle melanogenesis is coupled to the hair growth cycle, but that is not true for melanogenesis in the epidermis, which is continuous and is related to ultraviolet radiation.

In the telogen phase, hair follicle melanocytes do not proliferate and do not express tyrosinase and TRP-1; in the catagen phase, there is an interruption in melanin production and melanocytes undergo sudden apoptosis. It is during the anagen phase that resting melanocytes begin to proliferate, differentiate, and migrate within the hair follicle synchronously with the regeneration of the hair bulb. This is dependent on interaction between SCF and c-Kit, which activates transcription factors such as the microphthalmia transcription factor, which in turn stimulates transcription of tyrosinase, TRP-1, and DOPAchrome tautomerase (thereby increasing the production of melanin).

Three populations of melanocytes are present in hair follicles and each population expresses different molecules that determine hair and skin pigmentation:

- Hair bulb expresses TRP-2, Bcl-2, Pax3 and represents melanocyte stem cells. In the bulb, the most stem cells are not dependent on SCF/c-Kit to determine hair pigmentation, the number of melanocytes or their distribution.
- Outer root sheath keratinocytes form the bulge. It expresses c-Kit, TRP-1, and TRP-2. Proliferation of melanocytes occurs in it during early and intermediate anagen and melanin is produced.

– Hair matrix expresses c-Kit, TRP-1, TRP-2, and tyrosinase; melanocytes proliferate and synthesize melanin during intermediate anagen.

The dermal papilla is responsible for the secretion of growth factors such as SCF and hepatocyte growth factor, which by binding to their receptors in the outer root sheath and hair matrix, lead to the production of melanocytes and melanin³.

Mutations in various proto-oncogenes are involved in the pathophysiology of cancer, resulting in an increase in tyrosine kinase activity and leading to cell proliferation and the loss of control over the cell cycle.

Tyrosine kinase inhibitors are drugs that block the site where adenosine triphosphate binds to tyrosine residues of proto-oncogenes to prevent autophosphorylation and thereby inhibit the intracellular signal transduction that leads to cell proliferation and differentiation.

Imatinib is a first-generation TKI and dasatinib and nilotinib are second-generation TKIs (Table 1)⁴.

Tyrosine kinase inhibitors do not just block the tyrosine kinases of tumor cells; they also block those of cells that are normally found in the skin and its annexes.

Cutaneous adverse reactions are the most common non-hematologic adverse events caused by TKIs.

Edema (mainly facial) is the most frequently reported adverse effect for imatinib (39-65% of patients) and develops within six weeks of starting treatment. It develops because, by inhibiting the platelet-derived growth factor receptor, a dysregulation occurs in the interstitial fluid homeostasis and causes edema. It is usually mild to moderate^{5,6}.

Dermatitis or maculopapular rash is the second most common adverse effect produced by imatinib and the one most frequently reported in other

Table 1. FDA approved tyrosine kinase inhibitors and their therapeutic targets.

TKI name and family	Therapeutic target
Bcr-Abl TKIs	
Dasatinib	Bcr-Abl, Src family kinases, PDGFR- β , c-Kit, ephrin receptor kinases
Imatinib	Bcr-Abl, PDGFR- α and - β , c-Kit
Nilotinib	Bcr-Abl, PDGFR- α and - β , c-Kit, DDR 1 and 2
ErbB TKIs	
Erlotinib	EGFR
Gefitinib	EGFR
Lapatinib	EGFR (HER1) and HER2
VEGFR TKIs	
Axitinib	VEGFR-1, -2, -3; PDGFR, c-Kit
Pazopanib	VEGFR-1, -2, -3; PDGFR- α and - β , c-Kit
Sorafenib	C-Raf, B-Raf, c-Kit, FLT3, VEGFR-1, -2, -3, PDGFR- β
Sunitinib	PDGFR- α , PDGFR- β , VEGFR-1, -2, -3, c-Kit, RET, CSF-1R, FLT3
Vandetanib	VEGFR, EGFR, RET
Other TKIs	
Crizotinib	ALK, HGFR, c-Met
Ruxolitinib	JAK-1, JAK-2
Vemurafenib	B-Raf

Adapted from Josephs et al. Clinical pharmacokinetics of tyrosine kinase inhibitors: Implications for therapeutic drug monitoring. Ther Drug Monit. 2013;35:562-87.

second-generation TKIs such as dasatinib. It is dose-dependent and not frequent (7%) in patients receiving 25-140 mg/day of imatinib and more frequent (22-88%) in patients receiving doses of around 800 mg/day. It develops within eight weeks of starting treatment.

The third most common adverse event associated with TKIs (involving multi-targeted therapies), and of which there are few reports in the literature, is pigmentary changes in skin and hair. Onset of these changes in the pigmentation ostensibly begins about four weeks after the start of treatment.

Antitumor drugs in the TKI family for which hypopigmentation of the skin and hair have been described are dasatinib (in the family of Bcr-Abl), sunitinib, and pazopanib (VEGFR TKI family).



Figure 2. Hypopigmentation of hair and skin after five months of receiving chemotherapy with pazopanib.

Brazzelli, et al. reported the first case of a pediatric patient aged 16 years diagnosed with acute lymphoblastic leukemia who received a bone marrow transplant and was subsequently treated with dasatinib 100 mg twice a day. Four weeks after the start of therapy with dasatinib, he began to show achromic patches on his body and depigmentation of his hair, eyelashes, and eyebrows⁷.

Bible, et al. reported on a phase II study of 39 patients with metastatic thyroid cancer who were treated with pazopanib, 28 of whom developed hypopigmentation of the skin and hair. Pazopanib has been used for thyroid cancers resistant to other types of chemotherapy, as this class of TKI also blocks vascular endothelial growth factor (VEGF)⁸.

The pathophysiological basis of pigmentary alteration in patients treated with TKIs has not been well elucidated, but is thought to be based on the direct inhibition of the molecular target of c-Kit or the indirect inhibition of SCF production by stromal fibroblasts.

Adverse cutaneous reactions associated with TKIs are generally mild to moderate (CTCAE v3 grades 1 and 2) and it is not necessary to stop antitumor therapy; they resolve completely at the end of treatment.

It is important to identify and make the appropriate recommendations to patients about skin care and protection from the sun to prevent damage by ultraviolet radiation.

We present the cases of two patients who were seen at the Instituto de Cancerología who presented with adverse effects in hair and skin secondary to a multiple TKI (pazopanib).

CASE 1

A 48-year-old male patient with a family history of hereditary cancer: cervical cancer in the mother and breast cancer in a sister. He had a history of alcoholism since age 19, but had quit three years earlier and had systemic hypertension of five years duration, treated with losartan 50 mg every 12 hours.

He presented with biphasic synovial sarcoma in the right infraclavicular region of two years duration. The patient was phototype IV on the Fitzpatrick scale.

He was treated with three lines of treatment: cyclophosphamide, doxorubicin, and dacarbazine, then with ifosfamide, and finally with dacarbazine plus gemcitabine. In addition he received a course



Figure 3. Leukotrichia of the eyebrows and eyelashes.

of radiotherapy of 20 Gy in five fractions due to superior vena cava syndrome.

Fourth-line treatment with pazopanib 400 mg every 48 hours was initiated and hypopigmentation of skin and hair was documented since the eighth week (Fig. 2 and 3). At present he has been in treatment for seven months with partial response.

2. CASE 2

A 21-year-old male patient diagnosed with monophasic synovial sarcoma in his right foot in stage IV (soft tissue, bone, and lung metastases) and a time of disease evolution since diagnosis of two years. The patient was phototype III-IV on the Fitzpatrick scale.

He was treated with below-knee amputation, pulmonary metastasectomy, left temporal craniotomy, three cycles of adjuvant chemotherapy with doxorubicin plus ifosfamide, and five cycles with dacarbazine plus gemcitabine. He had disease progression with metastases in the thoracic and sacral spine so pazopanib 800 mg/day and adjuvant radiotherapy 30 Gy in 10 fractions were started. Generalized hypopigmentation developed six weeks after initiation of pazopanib (Fig. 5 and 6).

At the third month of treatment with pazopanib, a diagnosis of hypothyroidism was made and treatment with levothyroxine 25 mcg daily was started.



Figure 5. Hypopigmentation at 12 weeks after start of treatment with pazopanib.

In April 2014 he had disease progression in multiple sites: bone, lung, and pleura. Temozolomide 75 mg/m² was started. However, he continued to show progressive deterioration and one month later cardiac arrest and acute renal failure were documented and there was no response to resuscitation.



Figure 6. Scattered leukotrichia (left forearm).

DISCUSSION

As reported in the literature, these are the first reported cases of Mexican patients treated with pazopanib.

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