Hair Depigmentation During Chemotherapy With a Class III/V Receptor Tyrosine Kinase Inhibitor

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**Background:** Hair pigmentation is regulated by several factors including the interaction of the ligand stem cell factor (SCF) with its class III receptor tyrosine kinase, c-kit. An interruption of SCF/c-kit signal transduction results in hair depigmentation.

**Observations:** A 69-year-old white woman developed hair depigmentation and fine-textured hair while being treated with the phase I chemotherapeutic agent GW786034, a class III/V receptor tyrosine kinase inhibitor. Discontinuation of therapy resulted in a reversal of these hair changes.

**Conclusions:** Treatment with oral GW786034 resulted in reversible hair depigmentation and change in hair growth rate and texture, which were most likely due to an incomplete inhibition of SCF/c-kit signaling, although the exact mechanism is unknown. It would be intriguing to investigate topical tyrosine kinase inhibitors as a treatment for unwanted body hair.

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Each hair follicle cycle through 3 stages: growth (anagen), involution (catagen), and rest (telogen). During anagen, the pigmented hair shaft is formed. Hair pigmentation is dependent on the transfer of melanin produced in the neural crest-derived melanocytes to pre cortical hair matrix keratinocytes, which are then incorporated into the growing hair shaft. Hair pigmentation is tightly regulated by several factors including the interaction of the ligand stem cell factor (SCF) with its class III receptor tyrosine kinase, c-kit. The SCF/c-kit interaction is critical for pigment development during embryogenesis. Stem cell factor and c-kit map to the steel (Sl) and the white spotting (W) loci, respectively, and mutations in either of these genes result in depigmented hairs in mice. Also, administration of anti-c-kit antibody (ACK2) during murine embryonic development leads to coat depigmentation. In humans, piebaldism, an autosomal dominant disorder of melanocyte development characterized by leukoderma and poliosis, is associated with mutations to the c-kit gene. The SCF/c-kit interaction continues to be important for hair pigmentation postnatally, and interference in signal transduction results in hair depigmentation. Researchers now consider hair depigmentation a biological readout for pharmacological inhibition of c-kit in mice and in humans.

GW786034 is a tyrosine kinase inhibitor of vascular endothelial growth factor receptors (VEGFRs) 1, 2, 3; platelet-derived growth factor receptors α and β; and c-kit. It has antitumor and antiangiogenic activity in vitro and in vivo, and the pharmacokinetics and tolerability of oral GW786034 are currently being studied in patients with solid tumors. Initially it was thought that GW786034 selectively targeted VEGFRs, but recently it has been reported that c-kit is also targeted, as indicated by the adverse event of hair depigmentation reported in 6 of 14 patients receiving a dose greater than 800 mg/d.

**REPORT OF A CASE**

A 69-year-old white woman developed near complete hair depigmentation while being treated for metastatic renal cell carcinoma with the phase I chemotherapeutic agent, GW786034, a class III/V receptor tyrosine kinase inhibitor. The patient began to notice an increase in scalp hair loss and delayed hair regrowth after shaving her legs and axillae 2 months after initiating therapy with oral GW786034,
By the third month of therapy, nearly all of her scalp, body, and pubic hair began to grow white. In addition, she noticed a change in hair texture from coarse to fine. Prior to initiating therapy, the patient had coarse, black hair, which is verified by old photographs; she denies ever dying her hair and denies a history of alopecia.

On initial physical examination, the patient had a sharp demarcation of coarsely textured pigmented and finely textured depigmented hair of her scalp (Figure 1A). Her eyebrows were uniformly white, and she had fine, white hair on her body. She had no skin hypopigmentation or hyperpigmentation, and her nails and mucous membranes were normal. A hair mount showed a change from pigmented to depigmented hair; there also appeared to be a decrease in hair diameter in the area of depigmented hair (Figure 2). A scalp biopsy specimen revealed anagen and telogen hairs and evidence of follicular drop out and decreased pigment in the hair shaft. Findings from Fontana-Mason and melan-A staining to visualize melanin and melanocytes were negative. Therapy was discontinued after 8 months, and new hair growth was pigmented (Figure 1B).

COMMENT

This case report reinforces the importance of the SCF/c-kit pathway in melanocyte biology and highlights an important new cutaneous complication of chemotherapy. The adverse event of hair depigmentation seen in patients taking high-dose oral GW786034, including the patient presented in this case, is indicative of c-kit modulation, but the mechanism of hair depigmentation is not fully understood. Melanocyte proliferation, differentiation, and migration in anagen are dependent on the SCF/c-kit interaction, which results in signal transduction and activation of downstream transcription factors. The downstream effectors of c-kit signaling include microphthalmia, a transcription factor for the melanocyte lineage, and Slug, a zinc-finger transcription factor that results in pigmentation defects when altered. In this case, it is more likely that there is an inhibition of signal transduction with the administration of GW786034 vs a loss of melanocytes because pigment was produced with the discontinuation of treatment, thus indicating that melanocytes were present.

Another possibility for the hair depigmentation is dysfunction of the melanocyte. A similar chemotherapeutic medication to GW786034, SU11248, also inhibits class III/V receptor tyrosine kinases and has been found to cause reversible hair depigmentation when administered post-natally in both mice and humans. Interestingly, SU11248 has no effect on the level of c-kit–positive melanocytes associated with hair follicles, indicating that the inhibitory effect is at the level of melanocyte function rather than their development or survival. It is possible that a similar mechanism of melanocyte dysfunction is responsible for the GW786034-induced depigmentation.

In addition to hair depigmentation, this patient also experienced a change in hair texture from coarse to fine (Figure 2) and a reported history of delayed hair regrowth. This adverse event cannot be explained by the disruption of SCF/c-kit signal transduction, and it is likely a direct result of VEGFR inhibition. Vascular endothelial growth factor is an important component of follicular growth and cycling in mice. Vascular endothelial growth factor receptors 1, 2, and 3 are class V receptor tyrosine kinases that interact with VEGF to promote angiogenesis, monocyte chemotaxis, microvascular permeability, and vasodilation and to inhibit immature dendritic cells. It has been shown that VEGF increases hair growth in mice. The adverse event of hair regeneration seen in patients taking high-dose oral GW786034, including the patient presented in this case, is indicative of c-kit modulation, but the mechanism of hair regeneration is not fully understood. Melanocyte proliferation, differentiation, and migration in anagen are dependent on the SCF/c-kit interaction, which results in signal transduction and activation of downstream transcription factors. The downstream effectors of c-kit signaling include microphthalmia, a transcription factor for the melanocyte lineage, and Slug, a zinc-finger transcription factor that results in pigmentation defects when altered. In this case, it is more likely that there is an inhibition of signal transduction with the administration of GW786034 vs a loss of melanocytes because pigment was produced with the discontinuation of treatment, thus indicating that melanocytes were present.

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growth rate and follicular diameter and that VEGF messenger RNA is selectively up-regulated in follicular keratinocytes during the early and mid anagen growth phases. Blocking VEGF-mediated angiogenesis leads to delayed hair regrowth and reduced hair follicle size. Thus, the ability of GW786034 to potently inhibit VEGFR-1, -2, and -3 likely resulted in the patient’s delayed hair growth and decreased hair follicle diameter.

The ability of GW786034 to target both VEGFRs and c-kit has not been fully explained. We attribute the multitargeted action of GW786034 to similar ligand binding dimerization sites within the immunoglobulin-like domains of class III and class V receptor tyrosine kinases. Further investigation on the biochemical actions of GW786034 and related compounds on hair and pigment biology is warranted. Specifically, it would be intriguing to research the possible use of a topical receptor tyrosine kinase inhibitor as a treatment for unwanted body hair.

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References: