

## Hair Depigmentation and Vitiligo-like Lesions in a Leukaemic Paediatric Patient during Chemotherapy with Dasatinib

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Chronic myeloid leukaemia (CML) is the result of a fusion gene (BCR-ABL) which produces a constitutively activated tyrosine kinase (1). Tyrosine kinase inhibitors are used in the treatment of Philadelphia chromosome-positive (Ph-positive) haematological malignancies. Yet, the first generation of these drugs, including imatinib mesylate, has been associated with the development of treatment-resistant cases and drug intolerance. Improved understanding of the interaction between imatinib and its target led to the design of second-line tyrosine-kinase inhibitors, among which dasatinib and nilotinib are used in clinical practice (2, 3).

Dasatinib is an oral multi-target tyrosine-kinase inhibitor, which is able to inhibit the majority of imatinib-resistant BCR-ABL mutant forms, Src-family tyrosine kinases, c-Kit, ephrin-A2 receptor (EphA2R) and platelet-derived growth factor receptor- $\beta$  (PDGFR- $\beta$ ) (4).

The use of this drug has been approved for the treatment of CML in patients resistant or intolerant to previous therapies, and Ph-positive acute lymphoid leukaemia (ALL) (5). Cutaneous side-effects have rarely been reported in the literature (6, 7).

We report here a case of a paediatric patient affected by Ph-positive ALL who experienced the appearance of achromic patches on his neck and hands and complete depigmentation of his hair, eyelashes and eyebrows.

### CASE REPORT

A 16-year-old Caucasian male presented at the Paediatric Oncohaematology Department in September 2007 with a haemochromocytometric analysis characterized by leukocytosis, thrombocytopenia and moderate anaemia. A bone marrow needle aspiration biopsy showed a morphological pattern that allowed a diagnosis of ALL with a common immunophenotype (ALL L2), and the patient was initially treated with AIEOP LLA-R-2006 chemotherapeutic protocol (8).

One year later, a bone marrow aspiration revealed the presence of atypical cells, and a diagnosis of disease relapse with bone marrow localization was made; AIEOP LLA REC 2003 chemotherapeutic protocol was therefore administered (9).

In July 2008, a bone marrow cytogenetic analysis was performed, and the presence of Philadelphia chromosome-positivity was demonstrated; a cytofluorimetric analysis was also carried out, displaying the presence

of 0.05% cells with common immunophenotype, associated with early-B blast cells.

In light of these issues, one month later the patient underwent allogeneic umbilical cord haematopoietic stem cell transplantation.

One year after transplantation a second disease relapse occurred, and therapy with dasatinib 100 mg twice daily was started. Approximately 4 weeks after the start of therapy, the patient was first seen in the Dermatology Department for the appearance of achromic patches on his neck and the dorsal surfaces of his hands, and complete depigmentation of his hair, eyelashes and eyebrows (Fig. 1a). The patient reported no history of vitiligo, thyroid disorders and/or coeliac disease. Thyroid function testing was normal, and testing for autoimmunity disease was negative.

A photograph taken by the patient for his identity document one year previously showed his original phenotype: Fitzpatrick's skin phototype III, with dark eyes and hair (Fig. 1b).

Together, these clinical findings led us to make a diagnosis of skin and hair depigmentation during treatment with dasatinib.

### DISCUSSION

Very few cases of cutaneous adverse events of dasatinib are described in the literature; non-specific erythema-



Fig. 1. (a) Complete depigmentation of the hair, eyelashes and eyebrows during chemotherapy with dasatinib. (b) Patient's original phenotype (Fitzpatrick's skin phototype III). (Reproduced with the patient's permission.)

tous rashes, itch, skin exfoliation and irritation, pustular rashes and acne-like eruptions have been sparsely reported (11), as well as one case of recurrent neutrophilic panniculitis (12). To date, only a single case of skin and hair depigmentation in an adult patient affected by CML has been reported (13).

The case described here is noteworthy, because this is the first description of dasatinib-induced hair and skin depigmentation in a paediatric patient and the second description in a Caucasian patient, and emphasizes the role of the c-Kit pathway in melanocyte biology.

The proto-oncogene c-Kit is a gene encoding a class III tyrosine kinase receptor and has been mapped to the Dominant White Spotting (W) locus, while stem cell factor (SCF) is the ligand for c-Kit and has been mapped to the Steel (Sl) locus. It is now clear that the interaction between c-Kit and SCF plays an important role in the development of haematopoietic cells, germ cells, mast cells and melanocytes (13).

In particular, skin and hair pigmentation is tightly regulated by several factors; SCF exerts permanent survival, proliferation and migration functions in Kit receptor-expressing melanocytes, thus playing a crucial role in the development of melanocytes from their precursors in the embryonic neural crest cells during embryogenesis and maintenance of the melanocyte lineage in adult skin (14). As concerns hair follicle pigmentation, SCF and c-Kit interaction is a key event for survival of melanocytes during migration in the dermis, in the epidermal sheet prior to entering the hair follicles and survival of proliferating melanocytes in the anagen hair follicles (15).

In fact, mutations in either the *Sl* or *W* loci are known to produce effects on melanocyte survival and may result in unpigmented hair.

Although further investigation is required fully to understand the exact mechanism of hair depigmentation, the appearance of this cutaneous side-effect after chemotherapy with dasatinib is highly indicative of c-Kit modulation and blockade of SCF/c-Kit signal transduction.

The patient described here presented vitiligo-like patches localized on his upper extremities and neck, and complete depigmentation of the hair, eyelashes and eyebrows. Yet, the onset of those cutaneous side-effects did not represent a negative prognostic factor, nor imply the necessity for discontinuation of the treatment.

The increasingly common administration of kinase inhibitors in patients with different malignancies requires proper recognition of the adverse events of chemotherapy, thus it is important for the physician to become familiar with such cutaneous side-effects.

Further study of the mechanisms responsible for cutaneous depigmentation and the interference caused by tyrosine kinase inhibitors may provide important information about melanocyte pathophysiology and its implications in other cutaneous pathologies, such as vitiligo and melanoma.

*The authors declare no conflicts of interest.*

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