Skin Lesions in Patients Treated With Imatinib Mesylate: A 5-Year Prospective Study

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PRACTICE **POINTS**

- The most common cutaneous adverse reactions from imatinib mesylate (IM) are swelling and edema.
- Maculopapular rash with pruritus is one of the most common side effects from IM and can be effectively treated with oral or systemic antihistamines.
- The onset of periorbital edema requires a complete evaluation of renal function.

Imatinib mesylate (IM) represents the first-line treatment of patients with chronic myeloid leukemia (CLM) or gastrointestinal stromal tumor (GIST). It presents several side effects. However, less than 10% are nonhematologic including nausea, vomiting, diarrhea, muscle cramps, and cutaneous reactions. The aim of our study was to identify data regarding IM cutaneous adverse effects (AEs) to improve the clinical diagnosis and management of the more frequent side effects. Skin examination should be done before and during IM treatment so that AEs can be diagnosed and treated early with less impact on chemotherapy treatments and on the quality of life of the patient.

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Imatinib mesylate (IM) represents the first-line treatment of chronic myeloid leukemia (CML) and gastrointestinal stromal tumors (GISTs). Its pharmacological activity is related to a specific action on several tyrosine kinases in different tumors, including Bcr-Abl in CML, c-Kit (CD117) in GIST, and platelet-derived growth factor receptor in dermatofibrosarcoma protuberans.[1,2]

Imatinib mesylate has been shown to improve progression-free survival and overall survival[2]; however, it also has several side effects. Among the adverse effects (AEs), less than 10% are nonhematologic, such as nausea, vomiting, diarrhea, muscle cramps, and cutaneous reactions.[3,4]

We followed patients who were treated with IM for 5 years to identify AEs of therapy.

Methods

The aim of this prospective study was to identify and collect data regarding IM cutaneous side effects so that clinicians can detect AEs early and differentiate them from AEs caused by other medications. All patients were subjected to a median of 5 years' follow-up. We included all the patients treated with IM and excluded patients who had a history of eczematous dermatitis, psoriasis, renal impairment, or dyshidrosis palmoplantar. Before starting IM, all patients presented for a dermatologic

visit. They were subsequently evaluated every 3 months.

The incidence rate was defined as the ratio of patients with cutaneous side effects and the total patients treated with IM. Furthermore, we calculated the ratio between each class of patient with a specific cutaneous manifestation and the entire cohort of patients with cutaneous side effects related to IM.

When necessary, microbiological, serological, and histopathological analyses were performed.

Results

In 60 months, we followed 220 patients treated with IM. Among them, 55 (25%) developed cutaneous side effects (35 males; 20 females). The incidence rate of the patients with cutaneous side effects was 1:4. The median age of the entire cohort was 52.5 years. Fifty patients were being treated for CML and 5 for GISTs. All patients received IM at a dosage of 400 mg daily.

The following skin diseases were observed in patients treated with IM (Table): 19 patients with maculopapular rash with pruritus (no maculopapular rash without pruritus was detected), 7 patients with eczematous dermatitis such as stasis dermatitis and seborrheic dermatitis, 6 patients with onychodystrophy melanonychia (Figure 1), 5 patients with psoriasis, 5 patients with skin cancers including basal cell carcinoma (BCC)(Figure 2), 3 patients with periorbital edema (Figure 3), 3 patients with mycosis, 3 patients with dermatofibromas, 2 patients with dyshidrosis palmoplantar, 1 patient with pityriasis rosea–like eruption (Figure 4), and 1 patient with actinic keratoses on the face. No hypopigmentation or hyperpigmentation, excluding the individual case of melanonychia, was observed.

All cutaneous diseases reported in this study appeared after IM therapy (median, 3.8 months). The median time to onset for each cutaneous

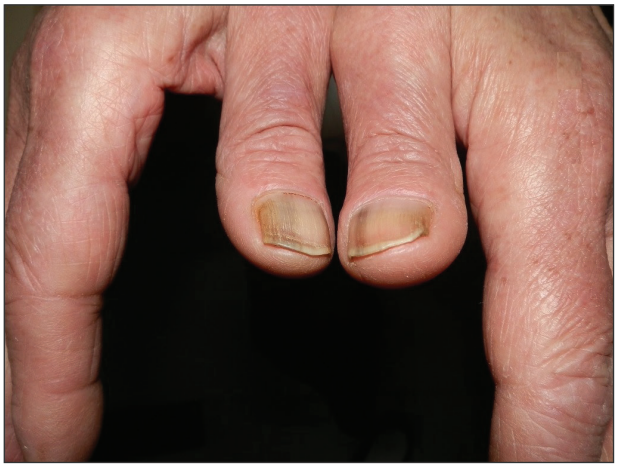

Figure 1. Melanonychia of the thumbs with slight onychodystrophy.

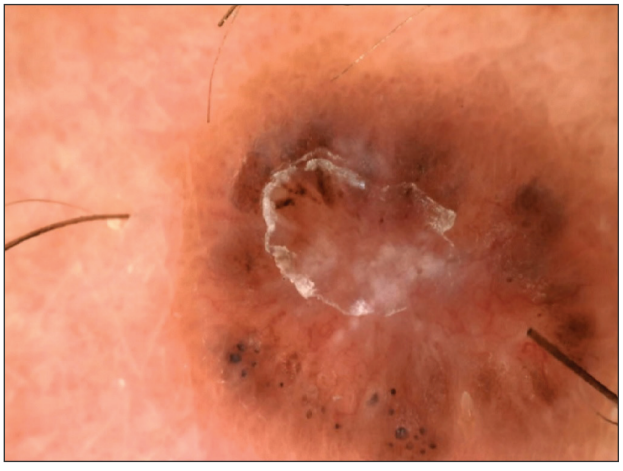

Figure 2. Basal cell carcinoma on dermoscopy showing large black-gray ovoid nests (original magnification ×40).

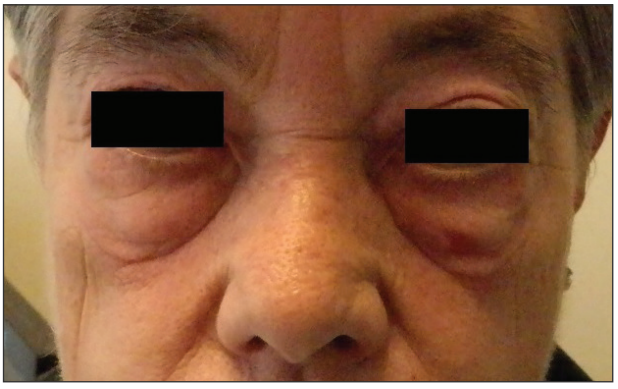

Figure 3. Periorbital edema in a woman.

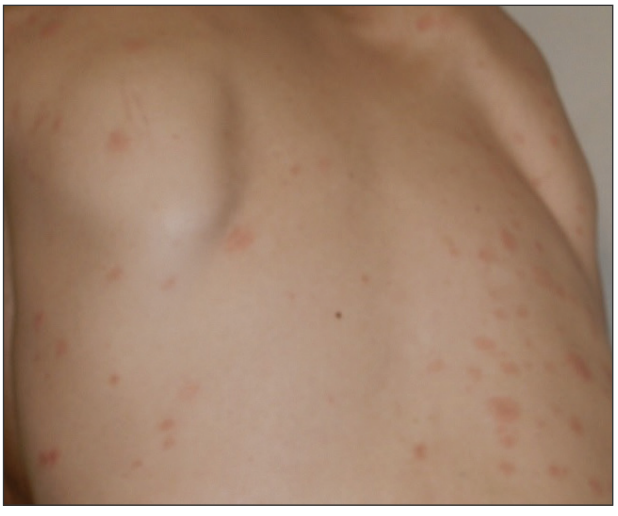

Figure 4. Macular rash resembling pityriasis rosea.

Skin Disease Observed in Patients Treated With IM

Skin Disease	No. of Patients	Median Time to Onset, mo	Incidence Rate[a]	Treatment
Maculopapular rash with pruritus	19	1.5	1:3	Only systemic antihistamines for low grades (eg, cetirizine, rupatadine, bilastine, ebastine)[b]; oral antihistamines (eg, cetirizine, rupatadine, bilastine, ebastine, hydroxyzine)[b] *plus* oral corticosteroids (eg, betamethasone, prednisolone, deflazacort)[c] for higher grades with hypereosinophilia
Eczematous dermatitis	7	3.3	1:8	Emollients (eg, oil-based products, vegetable shortening, barrier repair moisturizer with essential lipids) *plus* topical steroids (eg, methylprednisolone, hydrocortisone, diflucortolone valerate)[d] *plus* oral antihistamines[b]
Onychodystrophy melanonychia	6	4.2	1:9	Regression with suspension of the drug
Psoriasis	5	1.7	1:11	Emollients; topical steroid[d] and calcipotriol
Skin cancers (basal cell carcinoma)	5	4.0	1:11	Surgical excision
Periorbital edema	3	3.7	1:18	Diuretic therapy (eg, furosemide, hydrochlorothiazide, spironolactone)[e]; evaluate renal function, albumin, and CBC
Mycosis	3	4.1	1:18	Topical antifungal treatments (eg, clotrimazole, tioconazole, isoconazole nitrate–diflucortolone valerate cream)
Dermatofibromas	3	4.1	1:18	NA
Dyshidrosis palmoplantar	2	3.8	1:27	Emollients *plus* topical steroids[d] short therapy
Pityriasis rosea–like eruption	1	3.6	1:55	Suspension of treatment; evaluate CBC; exclude viral infection; if necessary, oral steroids[c]
Actinic keratoses on the face	1	3.9	1:55	Cryosurgery
Maculopapular rash without pruritus	0	NA	NA	Self-limiting; topical emollients and topical steroids[d]; no change in IM schedule
Total	55	3.8	1:4	NA

Abbreviations: IM, imatinib mesylate; CBC, complete blood cell count; NA, not applicable.

[a]Based on cohort with side effects (n=55).

[b]Antihistamines: cetirizine dosage at 10 mg daily (if renal failure, 5 mg daily); rupatadine shows better indications in urticarial reactions and in patients with a positive personal history for cardiologic problems; bilastine usually is used with the general dosage of 20 mg daily; ebastine dosage of 10 mg daily; hydroxyzine is preferred in case of higher grades of maculopapular rashes (oral administration at 25 mg daily or intramuscular 50–200 mg).

[c]Oral steroids: betamethasone dosage of 3 mg daily or prednisolone 1 mg/kg daily; deflazacort (6–90 mg daily, as initial dosage) in patients with diabetes mellitus.

[d]Topical steroids: methylprednisolone 1–2 times daily; hydrocortisone 1–2 times daily; diflucortolone valerate 1–2 times daily; topical association of betamethasone 0.5 mg and calcipotriol 50 μg.

[e]Diuretics: furosemide dosage of 25–50 mg daily; hydrochlorothiazide 25 mg daily; furosemide 20 mg combined with spironolactone 50 mg daily.

disorder is reported in the Table. During the first dermatologic visit before starting IM therapy, none of the patients showed any of these cutaneous diseases.

The adverse cutaneous reactions were treated with appropriate drugs. Generally, eczematous dermatitis was treated using topical steroids, emollients, and oral antihistamines. In patients with maculopapular rash with pruritus, oral corticosteroids (eg, betamethasone 3 mg daily or prednisolone 1 mg/kg) in association with antihistamine was necessary. Psoriasis was completely improved with topical betamethasone 0.5 mg and calcipotriol 50 μg. Skin cancers were treated with surgical excision with histologic examination. All treatments are outlined in the Table.

Imatinib mesylate therapy was suspended in 2 patients with maculopapular rash with moderate to severe pruritus; however, despite the temporary suspension of the drug and the appropriate therapies (corticosteroids and antihistamines), cutaneous side effects reappeared 7 to 10 days after therapy resumed. Therefore, the treatment was permanently suspended in these 2 cases and IM was replaced with erlotinib, a second-generation Bcr-Abl tyrosine kinase inhibitor.

Comment

The introduction of IM for the treatment of GIST and CML has changed the history of these diseases. The drug typically is well tolerated and few patients have reported severe AEs. Mild skin reactions are relatively frequent, ranging from 7% to 21% of patients treated.[3] In our case, the percentage was relatively higher (25%), likely because of close monitoring of patients, with an increase in the incidence rate.

Imatinib mesylate cutaneous reactions are dose dependent.[4] Indeed, in all our cases, the cutaneous reactions arose with an IM dosage of 400 mg daily, which is compatible with the definition of dose-independent cutaneous AEs.

The most common cutaneous AEs reported in the literature were swelling/edema and maculopapular rash. Swelling is the most common AE described during therapy with IM with an incidence of 63% to 84%.[5] Swelling often involves the periorbital area and occurs approximately 6 weeks after starting IM. Although its pathogenesis is uncertain, it has been shown that IM blocks the platelet-derived growth factor receptor expressed on blood vessels that regulates the transportation transcapillary. The inhibition of this receptor can lead to increased pore pressure, resulting in edema and erythema. Maculopapular eruptions (50% of cases) often affect the trunk and the limbs and are accompanied by pruritus. Commonly, these rashes arise after 9 weeks of IM therapy. These eruptions are self-limiting and only topical emollients and steroids are required, without any change in IM schedule. To treat maculopapular eruptions with pruritus, oral steroids and antihistamines may be helpful, without suspending IM treatment. When grade 2 or 3 pruriginous maculopapular eruptions arise, the suspension of IM combined with steroids and antihistamines may be necessary. When the readministration of IM is required, it is mandatory to start IM at a lower dose (50–100 mg/d), administering prednisolone 0.5 to 1.0 mg/kg daily. Then, the steroid gradually can be tapered.[6] Critical cutaneous AEs that are resistant to supportive measures warrant suspension of IM therapy. However, the incidence of this event is small (<1% of all patients).[7]

Regarding severe cutaneous AEs from IM therapy, Hsiao et al[8] reported the case of Stevens-Johnson syndrome. In this case, IM was immediately stopped and systemic steroids were started. Rarely, erythroderma (grade 4 toxicity) can develop for which a prompt and perpetual suspension of IM is necessary and supportive care therapy with oral and topical steroids is recommended.[9]

Hyperpigmentation induced by IM, mostly in patients with Fitzpatrick skin types V to VI and with a general prevalence of 16% to 40% in treated patients, often is related to a mutation of c-Kit or other kinases that are activated rather than inhibited by the drug, resulting in overstimulation of melanogenesis.[10] The prevalence of Fitzpatrick skin types I to III determined the absence of pigmentation changes in our cohort, excluding melanonychia. Hyperpigmentation was observed in the skin as well as the appendages such as nails, resulting in melanonychia (Figure 1). However, Brazzelli et al[11] reported hypopigmentation in 5 white patients treated with IM; furthermore, they found a direct correlation between hypopigmentation and development of skin cancers in these patients. The susceptibility to develop skin cancers may persist, even without a clear manifestation of hypopigmentation, as reported in the current analysis. We documented BCC in 5 patients, 1 patient developed actinic keratoses, and 3 patients developed dermatofibromas. However, these neoplasms probably were not provoked by IM. On the contrary, we did not note squamous cell carcinoma, which was reported by Baskaynak et al[12] in 2 CML patients treated with IM.

The administration of IM can be associated with exacerbation of psoriasis. Paradoxically, in genetically predisposed individuals, tumor necrosis factor α (TNF-α) antagonists, such as IM, seem to induce psoriasis, producing IFN-α rather than

TNF-α and increasing inflammation.[13] In fact, some research shows induction of psoriasis by anti–TNF-α drugs.[14-16] Two cases of IM associated with psoriasis have been reported, and both cases represented an exacerbation of previously diagnosed psoriasis.[13,17] On the contrary, in our analysis we reported 5 cases of psoriasis vulgaris induced by IM administration. Our patients developed cutaneous psoriatic lesions approximately 1.7 months after the start of IM therapy.

The pityriasis rosea–like eruption (Figure 4) presented as nonpruritic, erythematous, scaly patches on the trunk and extremities, and arose 3.6 months after the start of treatment. This particular cutaneous AE is rare. In 3 case reports, the IM dosage also was 400 mg daily.[18-20] The pathophysiology of this rare skin reaction stems from the pharmacological effect of IM rather than a hypersensitivity reaction.[18]

Deininger et al[7] reported that patients with a high basophil count (>20%) rarely show urticarial eruptions after IM due to histamine release from basophils. Premedication with an antihistamine was helpful and the urticarial eruption resolved after normalization in basophil count.[7]

Given the importance of IM for patients who have limited therapeutic alternatives for their disease and the ability to safely treat the cutaneous AEs, as demonstrated in our analysis, the suspension of IM for dermatological complications is necessary only in rare cases, as shown by the low number of patients (n=2) who had to discontinue therapy. The cutaneous AEs should be diagnosed and treated early with less impact on chemotherapy treatments. The administration of IM should involve a coordinated effort among oncologists and dermatologists to prevent important complications.

REFERENCES

1. Druker BJ, Talpaz M, Resta DJ, et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. *N Engl J Med*. 2001;344:1031-1037.
2. Scheinfeld N. Imatinib mesylate and dermatology part 2: a review of the cutaneous side effects of imatinib mesylate. *J Drugs Dermatol*. 2006;5:228-231.
3. Breccia M, Carmosimo I, Russo E, et al. Early and tardive skin adverse events in chronic myeloid leukaemia patients treated with imatinib. *Eur J Haematol*. 2005;74:121-123.
4. Ugurel S, Hildebrand R, Dippel E, et al. Dose dependent severe cutaneous reactions to imatinib. *Br J Cancer*. 2003;88:1157-1159.
5. Valeyrie L, Bastuji-Garin S, Revuz J, et al. Adverse cutaneous reactions to imatinib (STI571) in Philadelphia chromosome-positive leukaemias: a prospective study of 54 patients. *J Am Acad Dermatol*. 2003;48:201-206.
6. Scott LC, White JD, Reid R, et al. Management of skin toxicity related to the use of imatinibnmesylate (STI571, GlivecTM) for advanced stage gastrointestinal stromal tumors. *Sarcoma*. 2005;9:157-160.
7. Deininger MW, O'Brien SG, Ford JM, et al. Practical management of patients with chronic myeloid leukemia receiving imatinib. *J Clin Oncol*. 2003; 21:1637-1647.
8. Hsiao LT, Chung HM, Lin JT, et al. Stevens-Johnson syndrome after treatment with STI571: a case report. *Br J Haematol*. 2002;117:620-622.
9. Sehgal VN, Srivastava G, Sardana K. Erythroderma/ exfoliative dermatitis: a synopsis. *Int J Dermatol*. 2004; 43:39-47.
10. Pietras K, Pahler J, Bergers G, et al. Functions of paracrine PDGF signaling in the proangiogenic tumor stroma revealed by pharmacological targeting. *PLoS Med*. 2008;5:e19.
11. Brazzelli V, Prestinari F, Barbagallo T, et al. A long-term time course of colorimetric assessment of the effects of imatinib mesylate on skin pigmentation: a study of five patients. *J Eur Acad Dermatol Venerol*. 2007;21:384-387.
12. Baskaynak G, Kreuzer KA, Schwarz M, et al. Squamous cutaneous epithelial cell carcinoma in two CML patients with progressive disease under imatinib treatment. *Eur J Haematol*. 2003;70:231-234.
13. Cheng H, Geist DE, Piperdi M, et al. Management of imatinib-related exacerbation of psoriasis in a patient with a gastrointestinal stromal tumor. *Australas J Dermatol*. 2009;50:41-43.
14. Faillace C, Duarte GV, Cunha RS, et al. Severe infliximab-induced psoriasis treated with adalimumab switching. *Int J Dermatol*. 2013;52:234-238.
15. Iborra M, Beltrán B, Bastida G, et al. Infliximab and adalimumab-induced psoriasis in Crohn's disease: a aradoxical side effect. *J Crohns Colitis*. 2011;5:157-161.
16. Fernandes IC, Torres T, Sanches M, et al. Psoriasis induced by infliximab. *Acta Med Port*. 2011;24:709-712.
17. Woo SM, Huh CH, Park KC, et al. Exacerbation of psoriasis in a chronic myelogenous leukemia patient treated with imatinib. *J Dermatol*. 2007;34:724-726.
18. Brazzelli V, Prestinari F, Roveda E, et al. Pytiriasis rosea-like eruption during treatment with imatinib mesylate. description of 3 cases. *J Am Acad Dermatol*. 2005;53:240-243.
19. Konstantapoulos K, Papadogianni A, Dimopoulou M, et al. Pytriasis rosea associated with imatinib (STI571, Gleevec). *Dermatology*. 2002;205:172-173.
20. Cho AY, Kim DH, Im M, et al. Pityriasis rosealike drug eruption induced by imatinib mesylate (Gleevec). *Ann Dermatol*. 2011;23(suppl 3):360-363.