Actas Dermosifiliogr. 2014;105(7):655–662

ACTAS Dermo-Sifiliográficas

Full English text available at www.actasdermo.org

REVIEW

# Adverse Skin Effects of Imatinib, a Tyrosine Kinase Inhibitor☆

M. Pretel-Irazabal,[a,*] A. Tuneu-Valls,[b] N. Ormaechea-Pérez[b]

[a] *Departamento de Dermatología, Clínica Universidad de Navarra, Pamplona, Spain*
[b] *Departamento de Dermatología, Hospital de Donostia, San Sebastián, Spain*

Received 5 October 2012; accepted 13 January 2013
Available online 26 July 2014

**KEYWORDS**
Imatinib;
Adverse effect;
Skin

**Abstract** Imatinib mesylate is a tyrosine kinase inhibitor that targets the BCR-ABL, c-kit, and PDGF (platelet-derived growth factor) receptors. Imatinib is mainly indicated for chronic myeloid leukemia and gastrointestinal stromal tumors but is also prescribed by dermatologists for dermatofibrosarcoma protuberans, systemic sclerosis, and systemic mastocytosis, among other conditions. Most adverse effects are mild or moderate and therapy is generally well tolerated. Adverse skin effects are very common and include nonspecific manifestations such as edema and maculopapular rashes or eruptions of diverse types (lichenoid or psoriasiform lesions, acute generalized exanthematic pustulosis, Stevens-Johnson syndrome, and more). Identifying and properly treating these reactions can help optimize adherence to treatment and improve the prognosis of the underlying disease.


**PALABRAS CLAVE**
Imatinib;
Efecto adverso;
Piel

## Efectos adversos cutáneos del imatinib (inhibidor de la tirosín cinasa)

**Resumen** El imatinib mesilato es un inhibidor de la tirosín cinasa de administración oral que inhibe la BCR-abl, c-KIT y el *platelet-derived growth factor receptor* (PDGFR). Sus indicaciones fundamentales son la leucemia mieloide crónica y los tumores del estroma gastrointestinal. En Dermatología se emplea en enfermedades como el dermatofibrosarcoma protuberans, esclerosis sistémica y mastocitosis sistémica, entre otras. Es un fármaco en general bien tolerado, con la mayoría de efectos adversos leves o moderados. Los efectos secundarios dermatológicos son muy frecuentes e incluyen erupciones cutáneas inespecíficas como edema o erupciones maculopapulosas o con características clínicas distintivas (liquenoides, psoriasiformes, pustulosis exantemática aguda generalizada, síndrome de Stevens- Johnson. . .). Identificar y tratar correctamente estas reacciones puede ayudar a optimizar la adherencia del paciente al tratamiento y mejorar el pronóstico de su enfermedad de base.


☆ Please cite this article as: Pretel-Irazabal M, Tuneu-Valls A, Ormaechea-Pérez N. Efectos adversos cutáneos del imatinib (inhibidor de la tirosín cinasa). Actas Dermosifiliogr. 2014;105:655–662.
* Corresponding author.
*E-mail address:* mpretel@unav.es (M. Pretel-Irazabal).

1578-2190/$ - see front matter 

## Introduction

Imatinib mesylate (Glivec, Novartis; formerly known as STI 571) is an oral inhibitor of the tyrosine kinase BCR-Abl (a fusion protein from the Philadelphia chromosome, a cytogenetic abnormality of chronic myeloid leukemia [CML]), c-KIT, and platelet-derived growth factor receptor (PDGFR). The approval of this agent in 2001 by the US Food and Drug Administration revolutionized the treatment of patients with CML and significantly extended their overall survival.

Subsequently, the second generation of tyrosine kinase inhibitors nilotinib (Tasigna, Novartis) approved in 2007 and dasatinib (Sprycel; Bristol-Myers Squibb) approved in 2006, have extended the therapeutic options in patients intolerant of or resistant to imatinib.

Imatinib is also approved for treating other diseases such as unresectable *c-kit*$^+$ malignant gastrointestinal stromal tumors, acute Philadelphia chromosome$^+$ lymphoblastic leukemia, myelodysplastic syndromes with PDGFR gene reordering, hypereosinophilic syndrome, and chronic eosinophilic leukemia. In dermatology, the agent has proved effective in certain diseases such as inoperable or metastatic dermatofibrosarcoma protuberans (DFSP),[1] sclerodermous graft-versus-host disease,[2] systemic sclerosis,[3] systemic mastocytosis,[4] and melanoma with *c-kit*$^+$ mutations.[5] Table 1 shows the therapeutic targets in the different diseases in which imatinib has been used.

Doses of 400-600 mg/d are used in chronic CML and GIST. In accelerated CML and DFSP, a dose of up to 800 mg/d is indicated.

## Adverse Effects of Imatinib

Although the drug is generally well tolerated, up to 5.4% of patients have to discontinue treatment due to adverse effects.[6] Adverse effects are usually classified using the US National Cancer Institute scale, with 4 severity grades.[7] Most of the effects observed after administration of imatinib are mild or moderate in severity (grade 1 or 2).[8]

The grade 1 and 2 side effects most frequently observed after 5 years of follow-up in patients diagnosed for the first time with CML and treated with imatinib were edema, muscle cramps, diarrhea, nausea, musculoskeletal pain, skin rash and other skin conditions, abdominal pain, fatigue, joint pain, and headache.[8] Severe adverse effects, that is, grade 3 or 4 events, included neutropenia, thrombocytopenia, anemia, and liver enzyme elevation.[9]

Table 1 Therapeutic Targets in the Different Diseases in Which Imatinib Is Used.

| Chronic Lymphocytic Leukemia | Bcr-abl |
|---|---|
| Gastrointestinal stromal tumor | c-kit |
| Hypereosinophilic syndrome | FIP1L1-PDGFRα |
| Systemic mastocytosis | FIP1L1-PDGFRα |
| Chronic myelomonocytic leukemia | TEL-PDGFRβ |
| Dermatofibrosarcoma protuberans | COL1A1-PDGFβ |
| Melanoma | c-kit |

Imatinib appears to cause a higher rate of headache, diarrhea, vomiting, muscle spasm, and edema compared to other tyrosine kinase inhibitors.[10] However, imatinib is associated with a lower rate of skin rash, headache, pruritus, elevated transaminases, and alopecia. Hematologic adverse effects such as neutropenia were observed in 20% of patients compared to 12% with nilotinib. The 2 drugs caused similar rates of grade 3 and 4 thrombocytopenia and anemia.

Dasatinib appears to cause lower rates of nausea, vomiting, muscle inflammation, rash, fluid retention, and headaches compared to imatinib.[11] Similar percentages of grade 3 and 4 neutropenia and a higher rate of thrombocytopenia were observed with dasatinib compared to imatinib.[12] Table 2 shows a comparison of the percentage of patients with drug-related adverse skin effects.[13]

In general, any grade 3 or 4 adverse effect is managed by suspending administration and resuming at a lower dose once the toxicity has resolved.

In these patients, a careful assessment of the adverse effects is important because of the impact on treatment adherence and therefore efficacy. Adherence to treatment can essentially be improved by helping the patient to identify and manage side effects.

Table 2 Side Effects of the Different Tyrosine Kinase Inhibitors.

| Drug | Cutaneous Side Effects (% of Cases Treated) |
|---|---|
| Imatinib | Superficial edema (48-65)<br>Macular-papular eruption (~67)<br>Pigmentary disorders<br>Hypopigmentation/depigmentation (41)<br>Hyperpigmentation (~4)<br>Lichenoid reactions (IC)<br>Psoriasis and psoriasiform eruption (IC)<br>Pityriasis rosea-like eruption (IC)<br>Acute generalized exanthematous pustulosis (IC)<br>Stevens-Johnson syndrome (IC)<br>Urticaria (IC)<br>Neutrophilic dermatosis (IC)<br>Photosensitivity (IC)<br>Porphyria (IC)<br>Pseudoporphyria (IC) |
| Dasatinib | Rash (macular, papular, exfoliative) (11-27)<br>Mucositis/stomatitis (16)<br>Pruritus (11)<br>Panniculitis (IC) |
| Nilotinib | Rash (10-28)<br>Pruritus (17-24)<br>Cutaneous xerosis (13-17)<br>Alopecia (6) |

Abbreviation: IC, isolated case. Source: Adapted from Amitay-Laish et al.[13]

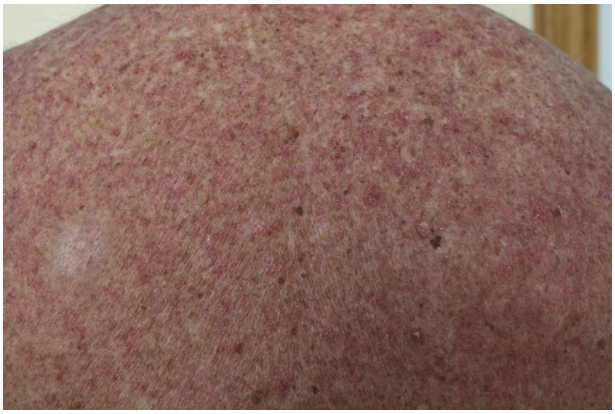

Figure 1 Seventy-year-old man diagnosed with gastrointestinal stromal tumor in treatment with imatinib for 3 months. Desquamative, pruritic macular-papular rash on the trunk and limbs.

## Adverse Cutaneous Effects of Imatinib

Skin rash is one of the most common adverse effects of imatinib, and estimates of incidence range from 7% to 88.9%.[14,15] Most cases are mild and self-limiting, with onset shortly after starting administration of the drug.[16] Table 3 shows classification of the most common adverse cutaneous effects according to their severity.[7] According to one study, 2.3% of patients treated at a dose of 400 mg/d and 5.3% of those treated at a dose of 800 mg/d[17] have severe adverse cutaneous effects.

The effects are thought to be independent of dose. A recent study reported such events in 7% of patients treated at a subtherapeutic dose of 25-140 mg/d and in 21% to 88% of patients treated with a dose of 400-800 mg/d.[18] This fact, along with the relatively low molecular weight of the drug, suggests that the cutaneous toxicity of imatinib is mediated by a toxic pharmacologic effect rather than an immunogenic effect.

Different types of skin reactions have been reported after using imatinib. These can be nonspecific, such as macular-papular rash, superficial edema, or pruritus, or less frequently, rash with clinically distinctive characteristics (lichenoid, psoriasiform, acute generalized exanthematous pustulosis, Stevens-Johnson syndrome [SJS], etc).

The most frequent adverse cutaneous effects associated with imatinib are described in the following sections.

### Macular-Papular Rash

Onset of rash caused by imatinib usually occurs a few days after starting treatment, although it can present after several months of treatment. According to some studies, rash is a frequent event and may present in up to 66.7% of patients within 2 months of starting the drug.[19]

The eruption is usually erythematous, macular-papular, sometimes desquamative, and pruritic (Fig. 1). The lesions are located on the forearms, trunk, and legs, and less often on the face.[20] They also present more frequently in patients who take high doses (> 600 mg/d) of the drug, and so the rash is thought of as a pharmacological toxicity rather than a hypersensitivity reaction.

Most cases of rash are self-limiting and readily treated with emollients, topical corticosteroids, and antihistamines. Dose reductions are therefore not needed. When the rash progresses to erythroderma, it is considered grade 4 toxicity, and suspension of the drug is indicated. In general, severe cases usually require treatment with oral corticosteroids and suspension of imatinib until the rash has improved to grade 1. Imatinib can then be reintroduced at a lower dose (50-100 mg/d) along with use of concomitant oral corticosteroids; the dose of imatinib can then be gradually increased.[20]

The initial recommended oral corticosteroid dose is usually 0.5-1 mg/kg of prednisone or equivalent. In certain patients, desensitization has been successful, suggesting that hypersensitivity mechanisms could also be present.[21]

In very severe cases, reintroduction of the drug is not recommended and replacement with nilotinib or dasatinib is recommended.

### Superficial Edema

One of the most frequent adverse cutaneous effects is superficial edema. According to several studies, between 48% and 65% of patients treated with this drug develop this complication within 6 weeks of starting treatment, often in association with weight gain.[15] Edema is normally mild to moderate in intensity, and presents on the face, and particularly the eyelids. It may be more severe in the mornings.[22] Edema of the limbs is much rarer. Central water retention (manifest as events such as pleural effusion and congestive heart failure) has also been reported in 1% to 3% of patients treated with imatinib.[23]

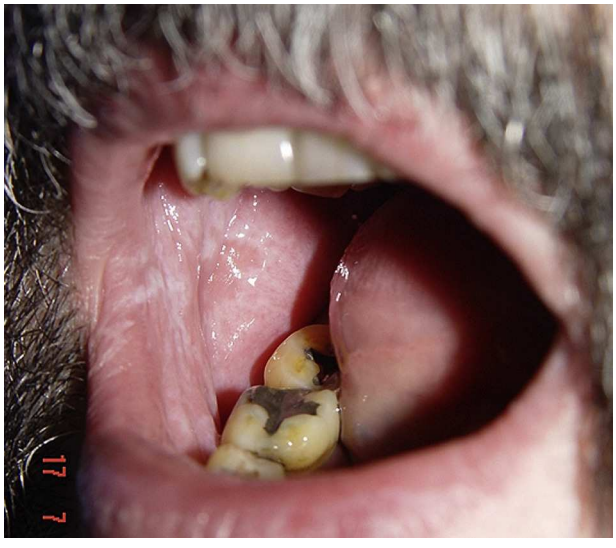

Figure 2 Fifty-one-year-old man diagnosed with chronic myeloid leukemia in treatment with imatinib for 1 month. Violaceous lichenoid lesions on the wrists and whitish plaques on the jugal mucosa, with histopathological diagnosis of mucosal lichen.

Table 3 Classification of Severity of Adverse Cutaneous Reactions Most Frequently Associated With Imatinib Use: United States National Cancer Institute Scale Version 4, Which Classifies Severity According to 4 Grades.

| | Adverse Effect | | | |
|---|---|---|---|---|
| **Grade** | **Macular-Papular Rash** | **Periorbital Edema** | **Skin Hyperpigmentation** | **Skin Hypopigmentation** |
| 1 | Macules/papules covering <10% body surface area with or without symptoms (eg pruritus, burning, tightness) | Soft or non-pitting | Hyperpigmentation covering< 10% of body surface area; no psychosocial impact | Hypopigmentation or depigmentation < 10% of body surface area; no psychosocial impact |
| 2 | Macules/papules covering 10%-30% body surface area with or without symptoms (eg, pruritus, burning, tightness); limiting instrumental activities of daily living | Indurated or pitting edema; topical intervention indicated | Hyperpigmentation > 10% of body surface area; psychosocial impact | Hypopigmentation or depigmentation > 10% of body surface area; psychosocial impact |
| 3 | Macules/papules covering >30% body surface area with or without associated symptoms; limiting self-care activities of daily living | Edema associated with visual disturbance; increased intraocular pressure, glaucoma or retinal hemorrhage; optic neuritis; diuretics indicated; operative intervention indicated | — | — |
| 4 | — | — | — | — |

Superficial edema is thought to be dose independent and arises as a result of increased pressure of interstitial dermal fluid caused by inhibition of PDGFR, which is responsible for interstitial fluid homeostasis.[24]

In most cases, management of superficial edema does not require the drug to be suspended or indeed any specific treatment. In some cases, a restriction of dietary salt and topical application of phenylephrine 0.25% may be beneficial.[25] In patients with central edema, diuretics may be indicated.[25]

## Lichenoid Reactions

Fifteen cases of lichenoid reactions have been reported in patients treated with imatinib.[26–29] The lesions occurred on the skin and/or mucosa (Fig. 2). These reactions appear to be dose dependent given that all reports were in patients who were receiving high doses of the drug (> 400 mg/d). In most cases, onset occurred from 1 to 3 months after starting treatment, although some patients did not develop the lesions until 1 year after starting imatinib. Suspension of the drug was not necessary in most patients, and the reactions were managed satisfactorily with the use of oral corticosteroids or acitretin.[30]

## Pigmentary Disorders

Several cases of pigmentary disorders due to the use of imatinib have been reported. Normally, hypopigmentation is manifest as hypochromic areas or diffuse or localized achromic areas, with remission after a dose reduction or discontinuation.[31,32]

Patients with dark phototypes are more likely to develop this adverse effect. Some studies have shown an incidence of hypopigmentation of 41% in patients treated for CML.[32]

Likewise, cases of hair depigmentation have been reported (Fig. 3).[33]

In addition, there have been case reports of patients treated with imatinib who develop skin, mucosal (hard palate), and nail hyperpigmentation.[34–37] In a study of 118 patients with CML treated with imatinib, only 4% developed hyperpigmentation.[32]

These reactions are likely to occur because imatinib inhibits c-KIT in the melanocytes, thereby reducing the activity of these cells and leading to hypopigmentation.[37]

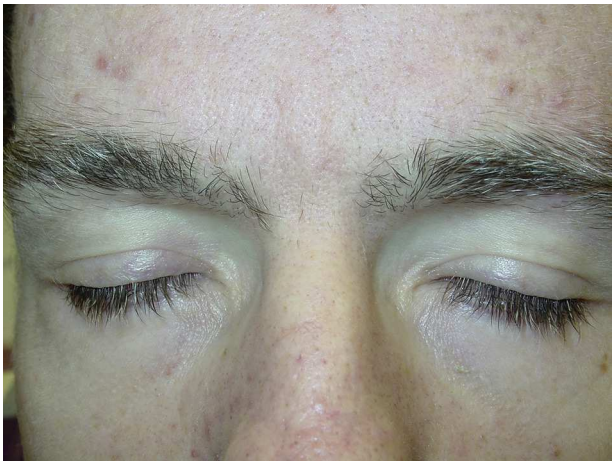

**Figure 3** Thirty-six-year-old man with *c-kit*$^{+}$ metastatic melanoma in treatment with imatinib for 3 years. Depigmentation of the hair follicles of the scalp, eyebrows, and eyelashes.

Moreover, imatinib can also cause hyperpigmentation by chelating one of its metabolites with iron and melanin in a mechanism similar to minocycline and antimalarial-associated hyperpigmentation.[38]

## Psoriasis and Psoriasiform Rash

In a study of 54 patients treated with imatinib, 4 developed psoriasiform rash between 1 and 7 months after starting treatment.[15] Half of these patients had a history of psoriasis. There have also been reports of imatinib-related exacerbation of psoriasis.[39,40] Deguchi et al.[41] reported psoriasiform palmoplantar hyperkeratosis and nail dystrophy after treatment with imatinib in 3 patients with no history of psoriasis. All patients improved after suspending or reducing the dose of the drug.

However, a case was published in which psoriasis improved in a patient with a GIST who started treatment with 400 mg/d of imatinib.[42]

T lymphocytes are known to play an important pathogenic role in psoriasis and imatinib can modulate T lymphocyte signalling.[43] The exact circumstances of the modulation are thought to influence whether a T-lymphocyte stimulatory or inhibitory effect occurs, leading to exacerbations or remissions, respectively, of the disease.

## Pityriasis Rosea-Like Rash

Several cases of rashes resembling pityriasis rosea have been reported in patients treated with imatinib. In most cases, rash onset was 1 to 2 months after starting treatment.[44]

In some cases, the relationship with imatinib seems fairly probable, as the skin lesions (clinically and pathologically consistent with pityriasis rosea) resolved after withdrawal of the drug and reappeared on rechallenge.[45,46]

The pathogenesis of this adverse effect is unknown.

## Acute Generalized Exanthematous Pustulosis

A case typical of acute generalized exanthematous pustulosis caused by imatinib has been reported.[47]

Subsequently, there were 3 reports of another 3 atypical cases in which an eruption with an atypical localization occurred between 1 and 4 years after starting the drug.[48–50]

Cases of acute generalized exanthematous pustulosis have not been reported in patients who received less than 600 mg/d of imatinib, and so this adverse effect is thought to be dose-dependent. The pathogenesis is not entirely understood.

## Stevens-Johnson Syndrome

Several cases of SJS have been reported in patients treated with imatinib.[51–55] Hsiao et al.[54] described a patient with CML who developed signs and symptoms reminiscent of SJS one week after starting the drug. These resolved after withdrawal of the drug and reappeared on rechallenge, strongly suggesting that the drug played a role in the eruption.

In other cases, however, the eruption did not appear after rechallenge at lower doses.[52]

In another case report of SJS, a patient treated with 400 mg/d of imatinib underwent rechallenge at a dose of 200 mg/d and the lesions reappeared.[55] At a second rechallenge at a dose of 100 mg/d and 1 mg/kg/d of prednisone, the lesions did not reappear. On suspending prednisone after 6 weeks, the imatinib dose was increased to 300 mg/d with no adverse effects.

Some authors suggest that desensitization should be attempted to manage these severe mucocutaneous eruptions when the lesions reappear even with concomitant use of prednisone.[21] Currently, with availability of alternatives such as dasatinib and nilotinib, we believe that switching to another drug is more appropriate in these cases.

## Neutrophilic Dermatoses

Two cases of Sweet syndrome have been reported in patients treated with imatinib, and in one case the temporal association was clear.[56,57] There has also been a report of a case of a patient with imatinib-induced neutrophilic eccrine hidradenitis,[47] 2 cases of erythema nodosum,[58] 3 cases of recurrent neutrophilic paniculitis,[59–61] and a case of neutrophilic foliculitis.[62]

## Toxic Epidermal Necrolysis

A case report has been published of a patient with CML who developed a very severe blistering skin and mucosal eruption after allogeneic bone marrow transplantation (with fludarabine and busulphan conditioning) and treatment with imatinib.[63] A causal relationship with imatinib is doubtful, as the patient was taking other drugs and the eruption appeared after 3 months of treatment with imatinib.

## Photosensitivity

Two studies have been published of several cases of photosensitivity in patients in long-term treatment with imatinib,[15,64] as well as a case of photo-induced dermatitis.[65]

## Other Skin Reactions

There have been case reports of fungoid-like mycosis,[66] cutaneous porphyria cutanea tarda,[67] pseudoporphyria,[68] and skin fragility and blistering[69,70] in patients treated with imatinib.

## Conclusion

Imatinib is a well-tolerated drug, although it is not devoid of adverse effects, some of which are serious. Cutaneous adverse reactions are among the most frequent side effects. In this article, we have exhaustively reviewed the side effects of this drug, paying particular attention to cutaneous effects, and we have provided guidance for their management. As this is a drug with many indications, including skin conditions, dermatologists are increasingly seeing patients in the clinic with adverse effects resulting from its use. Appropriate knowledge of these reactions and their management is of great importance, as adherence to treatment is essential to ensure efficacy in potentially fatal diseases such as CML.

## Ethical Responsibilities

**Protection of human and animal subjects.** The authors declare that no experiments were performed on humans or animals for this investigation.

**Confidentiality of data.** The authors declare that they have followed their hospital's protocol on the publication of data concerning patients and that all patients included in the study have received sufficient information and have given their written informed consent to participate in the study.

**Right to privacy and informed consent.** The authors declare that patient data do not appear in this article.

## Conflicts of Interest

The authors declare that they have no conflicts of interest.

## References


1. McArthur G. Molecularly targeted treatment for dermatofibrosarcoma protuberans. Semin Oncol. 2004;3:30–6.
2. Olivieri A, Locatelli F, Zecca M, Sanna A, Cimminiello M, Raimondi R, et al. Imatinib for refractory chronic graft-versus-host disease with fibrotic features. Blood. 2009;114:709–18.
3. Bournia VK, Evangelou K, Sfikakis PP. Therapeutic inhibition of tyrosine kinases in systemic sclerosis: A review of published experience on the first 108 patients treated with imatinib. Semin Arthritis Rheum. 2013;42:377–90.
4. Ustun C, DeRemer DL, Akin C. Tyrosine kinase inhibitors in the treatment of systemic mastocytosis. Leuk Res. 2011;35:1143–52.
5. Botella-Estrada R, Soriano V, Rubio L, Nagore E. KIT mutations in a series of melanomas and their impact on treatment with imatinib. Actas Dermosifiliogr. 2012;103:838–40.
6. Hochhaus A, O'Brien SG, Guilhot F, Druker BJ, Branford S, Foroni L, et al. Six-year follow-up of patients receiving imatinib for the first-line treatment of chronic myeloid leukemia. Leukemia. 2009;23:1054–61.
7. Common Terminology Criteria for Adverse Events (CTCAE). Version 4.0. Cancer Therapy Evaluation Program [Internet]. Bethesda: National Cancer Institute [citado 31 Oct 2012]. Disponible en: http://evs-nci.nih.gov/ftpl/CTCAE/About.html
8. Thanopoulou E, Judson I. The safety profile of imatinib in CML and GIST: Long-term considerations. Arch Toxicol. 2012;86:1–12.
9. Druker BJ, Guilhot F, O'Brien SG, Gathmann I, Kantarjian H, Gattermann N, et al. Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. N Engl J Med. 2006;355:2408–17.
10. Saglio G, Kim DW, Issaragrisil S, le Coutre P, Etienne G, Lobo C, et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. N Engl J Med. 2010;362:2251–9.
11. Kantarjian H, Shah NP, Hochhaus A, Cortes J, Shah S, Ayala M, et al. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med. 2010;362:2260–70.
12. Kantarjian H, Pasquini R, Hamerschlak N, Rousselot P, Holowiecki J, Jootar S, et al. Dasatinib or high-dose imatinib for chronic-phase chronic myeloid leukemia after failure of first-line imatinib: A randomized phase 2 trial. Blood. 2007;109:5143–50.
13. Amitay-Laish I, Stemmer SM, Lacouture ME. Adverse cutaneous reactions secondary to tyrosine kinase inhibitors including imatinib mesylate, nilotinib, and dasatinib. Dermatol Ther. 2011;24:386–95.
14. Basso FG, Boer CC, Correa ME, Torrezan M, Cintra ML, de Magalhães MH, et al. Skin and oral lesions associated to imatinib mesylate therapy. Support Care Cancer. 2009;17:465–8.
15. Valeyrie L, Bastuji-Garin S, Revuz J, Bachot N, Wechsler J, Berthaud P, et al. Adverse cutaneous reactions to imatinib (STI-571) in Philadelphia chromosome positive leukemias: a prospective study of 54 patients. J Am Acad Dermatol. 2003;48:201–6.
16. Mauro MJ, Deininger MW. Management of drug toxicities in chronic myeloid leukaemia. Best Pract Res Clin Haematol. 2009;22:409–29.
17. Verweij J, Casali PG, Zalcberg J, LeCesne A, Reichardt P, Blay JY, et al. Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: Randomised trial. Lancet. 2004;364:1127–34.
18. Brouard M, Saurat JH. Cutaneous reactions to STI571. N Engl J Med. 2001;345:618–9.
19. Marin D, Marktel S, Bua M, Armstrong L, Goldman JM, Apperley JF, et al. The use of imatinib (STI571) in chronic myeloid leukemia: Some practical considerations. Haematologica. 2002;87:979–88.
20. O'Brien S, Berman E, Moore JO, Pinilla-Ibarz J, Radich JP, Shami PJ, et al. NCCN Task Force Report. Tyrosine kinase inhibitor therapy selection in the management of patients with chronic myelogenous leukemia. J Natl Compr Canc Netw. 2011;9:S1–25.
21. Nelson RP, Cornetta K, Ward KE, Ramanuja S, Fausel C, Cripe LD. Desensitization to imatinib in patients with leukemia. Ann Allergy Asthma Immunol. 2006;97:216–22.
22. Guilhot F. Indications for imatinib mesylate therapy and clinical management. Oncologist. 2004;9:271–81.

23. Hensley ML, Ford JM. Imatinib treatment specific issues: related to safety, fertility and pregnancy. Semin Hematol. 2003;40:21–5.
24. Scheinfeld N. Imatinib mesylate and dermatology, part 2: A review of the cutaneous side effects of imatinib mesylate. J Drugs Dermatol. 2006;5:228–31.
25. Cornelison M, Jabbour EJ, Welch MA. Managing side effects of tyrosine kinase inhibitor therapy to optimize adherence in patients with chronic myeloid leukemia: The role of the midlevel practitioner. J Support Oncol. 2012;10:14–24.
26. Kuraishi N, Nagai Y, Hasegawa M, Ishikawa O. Lichenoid drug eruption with palmoplantar hyperkeratosis due to imatinib mesylate: a case report and a review of the literature. Acta DermVenereol. 2010;90:73–6.
27. Kawakami T, Kawanabe T, Soma Y. Cutaneous lichenoid eruption caused by imatinib mesylate in a Japanese patient with chronic myeloid leukaemia. Acta DermVenereol. 2009;89:325–6.
28. Ena P, Chiarolini F, Siddi GM, Cossu A. Oral lichenoid eruption secondary to imatinib (Glivec). J Dermatolog Treat. 2004;15:253–5.
29. Prabhash K, Doval DC. Lichenoid eruption due to imatinib. Indian J Dermatol Venereol Leprol. 2005;71:287–8.
30. Dalmau J, Peramiquel L, Puig L, Fernandez-Figueras MT, Roe E, Alomar A. Imatinib-associated lichenoid eruption: acitretin treatment allows maintained antineoplastic effect. Br J Dermatol. 2006;154:1213–6.
31. Grossman WJ, Wilson DB. Hypopigmentation from imatinib mesylate (Gleevec). J Pediatr Hematol Oncol. 2004;26:214.
32. Arora B, Kumar L, Sharma A, Wadhwa J, Kochupillai JWV. Pigmentary changes in chronic myeloid leukemia patients treated with imatinib mesylate. Ann Oncol. 2004;15:358–9.
33. Etienne G, Cony-Makhoul P, Mahon FX. Imatinib mesylate and gray hair. N Engl J Med. 2002;347:446.
34. Resende RG, Teixeira RG, Vasconcelos FD, Silva ME, Abreu MH, Gomez RS. Imatinib-associated hyperpigmentation of the palate in post-HSCT patient. J Craniomaxillofac Surg. 2012;40: e140–3.
35. Mattsson U, Halbritter S, Morner Serikoff E, Christerson L, Warfvinge G. Oral pigmentation in the hard palate associated with imatinib mesylate therapy: A report of three cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2011;111:e12–6.
36. McPherson T, Sherman V, Turner R. Imatinib-associated hyperpigmentation, a side effect that should be recognized. J Eur Acad Dermatol Venereol. 2009;23:82–3.
37. Wehrle-Haller B. The role of Kit-ligand in melanocyte development and epidermal homeostasis. Pigment Cell Res. 2003;16:287–96.
38. Kleinegger CL, Hammond HL, Finkelstein MW. Oral mucosal hyperpigmentation secondary to antimalarial drug therapy. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2000;90: 189–94.
39. Woo SM, Huh CH, Park KC, Youn SW. Exacerbation of psoriasis in a chronic myelogenous leukemia patient treated with imatinib. J Dermatol. 2007;34:724–6.
40. Cheng H, Geist DE, Piperdi M, Virk R, Piperdi B. Management of imatinib-related exacerbation of psoriasis in a patient with a gastrointestinal stromal tumour. Australas J Dermatol. 2009;50:41–3.
41. Deguchi N, Kawamura T, Shimizu A, Kitamura R, Yanagi M, Shibagaki N, et al. Imatinib mesylate causes palmoplantar hyperkeratosis and nail dystrophy in three patients with chronic myeloid leukaemia. Br J Dermatol. 2006;154:1216–8.
42. Miyagawa S, Fujimoto H, Ko S, Hirota S, Kitamura Y. Improvement of psoriasis during imatinib therapy in a patient with a metastatic gastrointestinal stromal tumour. Br J Dermatol. 2002;147:406–7.
43. Thachil J. T-regulatory cell response in psoriasis and changes with imatinib therapy. Clin Exp Dermatol. 2009;34:e1022.
44. Konstantopoulos K, Papadogianni A, Dimopoulou M, Kourelis C, Meletis J. Pityriasis rosea associated with imatinib (STI571, Gleevec). Dermatology. 2002;205:172–3.
45. Brazzelli V, Prestinari F, Roveda E, Barbagallo T, Bellani E, Vassallo C, et al. Pityriasis rosea-like eruption during treatment with imatinib mesylate: description of 3 cases. J Am Acad Dermatol. 2005;5:240–3.
46. Cho AY, Kim DH, Im M, Lee Y, Lee Y, Seo YJ, et al. Pityriasis rosea-like drug eruption induced by imatinib mesylate (Gleevec™). Ann Dermatol. 2011;23:360–3.
47. Dib EG, Ifthikharuddin JJ, Scott GA, Partilo SR. Neutrophilic eccrine hidradenitis induced by imatinib mesylate (Gleevec) therapy. Leuk Res. 2005;29:233–4.
48. Brouard MC, Prins C, Mach-Pascual S, Saurat JH. Acute generalized exanthematous pustulosis associated with STI571 in a patient with chronic myeloid leukemia. Dermatology. 2001;203:57–9.
49. Schwarz M, Kreuzer KA, Baskaynak G, Dorken B, le Coutre P. Imatinib-induced acute generalized exanthematous pustulosis (AGEP) in two patients with chronic myeloid leukemia. Eur J Haematol. 2002;69:254–6.
50. Gambillara E, Laffitte E, Widmer N. Severe pustular eruption associated with imatinib and voriconazole in a patient with chronic myeloid leukemia. Dermatology. 2005;211:363–5.
51. Vidal D, Puig L, Sureda A, Alomar A. Sti571-induced Stevens-Johnson syndrome. Br J Haematol. 2002;119:274–5.
52. Pavithran K, Thomas M. Imatinib induced Stevens-Johnson syndrome: Lack of recurrence following re-challenge with a lower dose. Indian J Dermatol Venereol Leprol. 2005;71:288–9.
53. Hsieh HJ, Chan AL, Lin SJ. Stevens-Johnson syndrome induced by combination of imatinib and allopurinol. Chemotherapy. 2009;55:197–9.
54. Hsiao LT, Chung HM, Lin JT, Chiou TJ, Liu JH, Fan FS, et al. Stevens-Johnson syndrome after treatment with STI571: A case report. Br J Haematol. 2002;117:620–2.
55. Mahapatra M, Mishra P, Kumar R. Imatinib-induced Stevens-Johnson syndrome: recurrence after re-challenge with a lower dose. Ann Hematol. 2007;86:537–8.
56. Ayirookuzhi SJ, Ma L, Ramshesh P, Mills G. Imatinib-induced Sweet syndrome in a patient with chronic myeloid leukemia. Arch Dermatol. 2005;141:368–70.
57. Liu D, Seiter K, Mathews T, Madahar CJ, Ahmed T. Sweet's syndrome with CML cell infiltration of the skin in a patient with chronic-phase CML while taking imatinib mesylate. Leuk Res. 2004;28:61–3.
58. Drummond A, Micallef-Eynaud P, Douglas WS, Hay I, Holyoake TL, Drummond MW. A spectrum of skin reactions caused by the tyrosine kinase inhibitor imatinib mesylate (STI571, Glivec). Br J Haematol. 2003;120:911–3.
59. De Masson A, Bouvresse S, Clérici T, Mahé E, Saïag P. Recurrent neutrophilic panniculitis in a patient with chronic myelogenous leukaemia treated with imatinib mesilate and dasatinib. Ann Dermatol Venereol. 2011;138:135–9.
60. Assouline S, Laneuville P, Gambacorti-Passerini C. Panniculitis during dasatinib therapy for imatinib-resistant chronic myelogenous leukemia. N Engl J Med. 2006;354:2623–4.
61. Ugurel S, Lahaye T, Hildenbrand R, Glorer E, Reiter A, Hochhaus A, et al. Panniculitis in a patient with chronic myelogenous leukaemia treated with imatinib. Br J Dermatol. 2003;149:678–9.
62. García-Romero MT, Durán-McKinster C, de Ocariz MS, Carrasco-Daza D, Palacios-López C, Orozco-Covarrubias L, et al. Imatinib mesylate-induced neutrophilic folliculitis in a teenager. Int J Dermatol. 2012;51:1529–30.
63. Schaich M, Schäkel K, Illmer T, Ehninger G, Bornhäuser M. Severe epidermal necrolysis after treatment with imatinib and consecutive allogeneic hematopoietic stem cell transplantation. Ann Hematol. 2003;82:303–4.

64. Rousselot P, Larghero J, Raffoux E, Calvo F, Tulliez M, Giraudier S, et al. Photosensitization in chronic myelogenous leukemia patients treated with imatinib mesylate. Br J Haematol. 2003;120:1091–2.
65. Brazzelli V, Muzio F, Manna G, Moggio E, Vassallo C, Orlandi E, et al. Photoinduced dermatitis and oral lichenoid reaction in a chronic myeloid leukemia patient treated with imatinib mesylate. Photodermatol Photoimmunol Photomed. 2012;28:2–5.
66. Clark SH, Duvic M, Prieto VG. Mycosis fungoides-like reaction in a patient treated with Gleevec. J Cutan Pathol. 2003;30:279–81.
67. Ho AY, Deacon A, Osborne G, Mufti GJ. Precipitation of porphyria cutanea tarda by imatinib mesylate? Br J Haematol. 2003;121:375.
68. Timmer-de Mik L, Kardaun SH, Kramer MH, Hayes DP, Bousema MT. Imatinib-induced pseudoporphyria. Clin Exp Dermatol. 2009;34:705–7.
69. Reddy H, Horne HL, Maung Z. Skin fragility and blistering secondary to imatinib. Clin Exp Dermatol. 2012;37:572–3.
70. Verma SM, Murphy G. Skin fragility and blistering with imatinib mesylate. J Eur Acad Dermatol Venereol. 2010;24:496–8.