

# Severe toxicity of skin rash, fever and diarrhea associated with imatinib: case report and review of skin toxicities associated with tyrosine kinase inhibitors

Xuan Huang<sup>1</sup>  
Samir Patel<sup>2</sup>  
Nasir Ahmed<sup>2</sup>  
Karen Seiter<sup>2</sup>  
Delong Liu<sup>2</sup>

<sup>1</sup>Department of Medicine, Richmond University Medical Center, New York, NY, USA; <sup>2</sup>Division of Oncology and Hematology, New York Medical College and Westchester Medical Center, New York, NY, USA

**Abstract:** Chronic myeloid leukemia (CML) is characterized by a Philadelphia chromosome which contains an oncogene, *bcr-abl*. This oncogene encodes a tyrosine kinase which is constitutively activated. Imatinib, a tyrosine kinase inhibitor (TKI), has been widely used in the treatment of CML. Dasatinib and nilotinib were recently approved for the treatment of CML. Other TKIs, such as bosutinib, erlotinib, and sunitinib, are under study for the treatment of CML as well as other hematologic and solid malignancies. Skin rash has been reported as one of the most common side effects of the TKIs. Here we present a case of severe skin rash together with unusual symptoms of high fever and diarrhea induced by imatinib in a CML patient. The dermatologic toxicities from a variety of tyrosine kinase inhibitors are reviewed and general principles of management are also discussed.

**Keywords:** chronic myeloid leukemia, skin rash, tyrosine kinase inhibitor, imatinib

## Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative disorder involving the clonal expansion of transformed hematopoietic progenitor cells. It is characterized by a reciprocal translocation between the long arms of chromosomes 9 and 22 which generate the Philadelphia chromosome (Ph) (Faderl et al 1999). This leads to formation of the *Bcr-Abl* oncogene which encodes the Bcr-Abl protein, leading to constitutive activation of the Abl tyrosine kinase (Nowell 2007). Imatinib mesylate, the first selective tyrosine kinase inhibitor targeting Bcr-Abl protein, has shown clinical efficacy in the treatment of CML by inducing complete remission and decreased mortality of CML patients. Since the approval of imatinib in 2001, dasatinib and nilotinib have been approved for use in imatinib-resistant or -intolerant CML cases (Madhusudan and Ganesan 2004; Ottmann et al 2005; Kantarjian et al 2006). Numerous other tyrosine kinase inhibitors (including anti-EGFRs and anti-VEGFRs) are under study for the treatment of hematologic and solid tumor malignancies. The most common side effects of these kinase inhibitors include myelosuppression, nausea, vomiting, diarrhea, and skin rashes (Schwab 2006). Here we report a case of severe, diffuse body rash together with unusual symptoms of fever and diarrhea in a patient with newly diagnosed CML after treatment with imatinib.

## Case report

A 77-year-old female was found to have elevated white blood cell count (WBC) count on routine physical examination with lab tests. Her past medical history includes osteoporosis, Meniere's disease, hypercholesterolemia, cholecystectomy, and appendectomy.

Correspondence: Delong Liu  
Division of Oncology and Hematology,  
New York Medical College and  
Westchester Medical Center, Munger  
Pavilion 250, Valhalla, NY 10595, USA  
Tel +1 914 493 7514  
Fax +1 914 594 4420  
Email delong\_liu@nymc.edu

She has a history of allergy to codeine and clarithromycin. She had normal functional status at the first office visit. Physical examination was unremarkable with no palpable hepatosplenomegaly or lymphadenopathy. Her WBC count was 31,500/ $\mu\text{L}$ , hemoglobin was 12.5 gm/dL, hematocrit was 37.2%, and platelet count was 415,000/ $\mu\text{L}$ . Bone marrow revealed myeloid hyperplasia, and all metaphases had karyotype of t(9; 22) translocation. There were less than 1% of myeloblasts and 19% promyelocytes. A diagnosis of CML in chronic phase was established. She was started on imatinib (Gleevec) 400 mg daily. 12 days after initiation of imatinib, she presented to the clinic complaining of profound malaise, progressive weight loss, high fever to 103 °F (39 °C), nausea, vomiting, and generalized skin rashes with no arthralgia or arthritis (Figure 1). The rashes were patchy, and papulomacular in shape involving trunk and all extremities. At that time, WBC count was 35,700/ $\mu\text{L}$  with no eosinophilia. She was admitted to the Westchester Medical Center and continued to have high fevers. Imatinib was discontinued. The patient was treated with vancomycin and ceftazidime. All microbiologic cultures were repeatedly negative.

Other infectious etiologies were also ruled out (including Lyme disease, Ehrlichiosis, and babesiosis). Fever, diarrhea, and rashes subsequently resolved after 4 days. At the outpatient evaluation one week later, the patient remained well with no residual symptoms. Imatinib 400 mg daily was resumed. Within hours of the first dose, the patient experienced recurrent fever, chills and similar rashes. Skin biopsy was not performed. Imatinib was immediately stopped and rash again resolved later. Her blood count at 2-week follow up evaluation revealed WBC 6,200, hemoglobin 10.4 and platelets 433,000. Bone marrow re-evaluation showed 1% blast and Ph+ in 14 out of 20 cells examined (70% Ph+). She was then enrolled in investigational studies (the result will be published separately) (Gontarewicz et al 2007; Paquette et al 2007; Tauchi et al 2007).

## Discussion

The current case had grade 4 toxicity including skin rashes as well as high fever, vomiting, and diarrhea leading to dehydration after ingestion of imatinib. DRESS syndrome (drug rash/reaction with eosinophilia and systemic symptoms,



**Figure 1** Skin rashes after ingestion of imatinib. The rashes were patchy and papulomacular in shape.

drug hypersensitivity syndrome) is among the differential diagnosis (Sullivan and Shear 2001), even though this case does not have the full features of the syndrome due to the absence of internal organ damage (hepatitis) and eosinophilia. It has been shown that imatinib is responsible for grade 1–2 skin rashes in 30% to 40% of the patients (O'Brien et al 2003; Druker et al 2006). Although rare vasculitis and Stevens-Johnson syndrome have been reported in a few cases, skin rash associated with imatinib is generally mild, and is most often characterized by macropapular lesions occurring most prominently on the forearms, trunk, and occasionally on the face (Guilhot 2004). Grade 3–4 rash was seen in 2% to 5% of patients in 2 studies (O'Brien et al 2003; Guilhot 2004). Severe grade 4 toxicities including skin, GI, and high fever in a single patient has not been reported. Hair depigmentation and periorbital edema are two other cutaneous abnormalities associated with imatinib (Robert et al 2005).

As small molecules of tyrosine kinase inhibitors gradually arise as treatments for patients with CML and other malignancies, the safety of these drugs becomes an important issue. The dermatologic side effects of dasatinib were observed in START A, B, C and L trials in a total of 789 patients with CML of all phases (Anon 2006). Lower incidence of skin rash (11% and 15%) was found in patients with blast crisis (myeloid and lymphoid, respectively), compared with 22% and 27% of the patients with accelerated and chronic phases of CML (Anon 2006). Most of these rashes were grade 1–2. A rare presentation of painful subcutaneous nodules with overlying erythema (panniculitis) was described in two patients with chronic phase CML resistant to imatinib (Assouline et al 2006). In both cases, no cutaneous side effects were noticed during previous imatinib treatment (Assouline et al 2006). Nilotinib yields comparable results of rash occurrence with dasatinib and it is sometimes associated with dry skin. Another promising option for CML patients who are resistant to imatinib is bosutinib (SKI-606). In one of the clinical trials in patients with CML or ALL, grade 1–2 rashes were noticed in 13% of the patients and grade 3–4 rashes were found in 6% of the patients (Gambacorti-Passerini et al 2007).

Epidermal growth factor receptor (EGFR) inhibitors, eg, erlotinib, gefitinib, panitumumab, are well known to induce dramatic skin rashes and other characteristic cutaneous changes such as curling of hair and eyelashes, periungual paronychia, and xerosis (Agero et al 2006). Tyrosine kinase inhibitors, including the Bcr-Abl kinase inhibitors imatinib and dasatinib, generate milder and less significant skin/cutaneous side effects. It appears that the cutaneous

side effects of Bcr-Abl kinase inhibitors are rather different from those of EGFR inhibitors in terms of distribution and morphology (Table 1). The rash associated with erlotinib usually ranges from simple inflammatory papules and pustules on the scalp, face, neck and upper trunk (previously termed “acne-like, acneiform”), to unusual vasculitis (Agero et al 2006). Incidence of mild-moderate (grade 1–2) skin rash was reported from 59% to 82% (Hidalgo et al 2001; Segaeert and Van Cutsem 2005; Journagan and Obadiab 2006). More severe forms such as hemorrhagic-necrotic type leukocytoclastic vasculitis were described in two patients with advanced hepatocellular carcinoma and metastatic pancreatic cancer treated with erlotinib (Boeck et al 2007). Paronychia inflammation, curly hair and eyelashes (Agero et al 2006), xerosis (Agero et al 2006), and frontal alopecia (Robert et al 2005) were also frequently described.

Hand-foot syndrome (HFS), synonymous with hand-foot skin reaction and palmar-plantar erythrodysesthesia, is a distinct cutaneous manifestation associated with sorafenib, sunitinib, and lapatinib (Adams and Leggas 2007; Chu et al 2007; Strumberg et al 2007). Approximately 13% and 18% of patients experienced grade 1–2 HFS, and 4% and 8% of patients experience grade 3–4 HFS during the course of sunitinib and sorafenib treatment, respectively (Adams and Leggas 2007; Strumberg et al 2007). HFS appears to occur more often when lapatinib and capecitabine were combined (Chu et al 2007). It is likely that capecitabine contributes to the development of HFS, which has already been shown to be a dose-limiting toxicity of capecitabine (Gressett et al 2006). In addition to alopecia and splinter subungual hemorrhages, which are induced by both sorafenib and sunitinib in a subgroup of patients, sunitinib can also lead to skin discoloration (Robert et al 2005; Adams and Leggas 2007). Similar to imatinib, hair depigmentation and periorbital edema are also seen with sunitinib treatment (Robert et al 2005; Adams and Leggas 2007).

Although skin rash occurs quite often during treatment with tyrosine kinase inhibitors, there are insufficient evidence-based data to establish guideline on the management of this side effect. Due to their substantial clinical benefit, continuation of therapy is preferred while the skin rash and other side effects are aggressively managed. In these cases, topical antiseptics, topical antibiotics (eg, 1% clindamycin), and topical steroids have been used (Agero et al 2006; Tsai et al 2006). Topical immunomodulatory agents such as pimecrolimus have also been used occasionally (Agero et al 2006). In more severe situations, systemic antibiotics may be necessary since *Staphylococcus aureus* may supervene,

**Table 1** Incidence and management of skin rash and other cutaneous side effects associated with tyrosine kinase inhibitors

	Grade 1, 2 skin rash	Grade 3, 4 skin rash	Other cutaneous abnormalities	Management
Imatinib	30%–40% rash (Schwab, Druker)	3%–5% (Guilhot); 2% (Schwab); Rare vasculitis, Stevens-Johnson syndrome, toxic epidermal necrosis (Guilhot)	Hair repigmentation (Roberts); periorbital edema (Roberts)	Initially discontinue with or without topical/systemic steroids; then either restart imatinib with concomitant short-term steroids therapy, or restart imatinib with gradual dose escalation (Rul)
Dasatinib	27% (START-A, Anon); 11% (START-B, Anon); 22% (START-C, Anon); 15% (START-L, Anon)		Panniculitis (Painful subcutaneous nodules with overlying erythema) (Assouline)	Discontinue, restart with concomitant steroids after rash resolved (Assouline)
Nilotinib	27% (Schwab); 17% (Kantarjian)	<1% (5); 4% (Schwab)	Dry skin	
Bosutinib	13% (Gambacorti)	6% (Gambacorti)		
Erlotinib	75% (package insert); 59%–82% (Hidalgo); 67%–79% (Segaert); 77% (Journagan)	35%–50% (Wacker); 2.6% (Segaert)	Paronychia inflammation; curly hair and eyelashes (Agero); Xerosis (Agero); frontal alopecia (Roberts)	Mild: continue tx; severe: drying agents, topical antiseptics, topical antibiotics (clindamycin), systemic antibiotics (clindamycin, minocycline), topical steroids (tretinoin), topical immunomodulatory agents (pimecrolimus) and short term topical steroids or systemic steroids (Agero)
Lapatinib	26% rash; 41% HFS (package insert, Chu)	2% rash; 12% HFS (package insert, Chu)	Xerosis, pruritus, alopecia (package insert, Chu)	
Sorafenib	18% HFS (Strumberg); 24% rash (Strumberg)	8% HFS (Strumberg); 2% rash (Strumberg)	18% Alopecia (Strumberg); splinter subungual hemorrhages (Roberts)	Dose reduction and interruption
Sunitinib	14% rash; 13% HFS (Adams); seborrheic dermatitis-like rash (Tsai)	1% rash (Adams); 4% HFS (Adams)	5% alopecia; 8% hair depigmentation; 30% skin discoloration (Adams); periorbital edema (Roberts); splinter subungual hemorrhages (Roberts)	Topical 0.1% mometasone furoate ointment and discontinuation of sunitinib (Tsai)

**Abbreviations:** Tx, therapy; HFS, hand-foot syndrome.

causing secondary bacterial infection (Agero et al 2006). Oral tetracycline 250 mg 4 times daily or minocycline 100 mg two times daily appears to be a suitable regimen (Agero et al 2006). Short-term systemic steroids may also be very useful, especially in patients with grade 3 or 4 rashes. The acceptable strategy is initial dose reduction or interruption, followed by either reinitiation of kinase inhibitors with concomitant short-term steroids therapy. It appears 30 mg or 50 mg prednisone per day for two weeks offered good protection (Rule et al 2002; Assouline et al 2006). The prednisone can be gradually tapered off (Rule et al 2002) or to a maintenance dose of 5 mg per day for the duration of the course of treatment (Assouline et al 2006), depending on the likelihood of recurrence of skin rash. Another strategy, which has been used quite often is the reinitiation with gradual dose

escalation to the level which can be tolerated by the patients (Rule et al 2002; Assouline et al 2006). However, there is significant concern about the efficacy of lower doses of kinase inhibitors. Skin rash usually disappears after discontinuation of tyrosine kinase inhibitor. In severe cases, it will resolve in a couple of days with the administration of either topical or systemic medications.

The development of skin rash related to EGFR tyrosine kinase inhibitors seems to have an important implication in the efficacy of the treatment. The appearance of skin rash in patients with non-small cell lung cancer and pancreatic cancer treated with erlotinib is strongly associated with longer survival, and the overall survival is increased with the rash severity (Wacker et al 2007). This leads to the notion that induction of skin rash by dose escalation may

correlate with higher efficacy of tyrosine kinase inhibitors in the treatment of malignancies. Further understanding of the underlying mechanisms leading to the development of the rashes from different class of TKIs may assist us in finding new drug targets and modify the current therapies to a level of maximal efficacy.

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## Disclosures

The authors have no conflicts of interest to disclose.

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