

Nilotinib induced skin rash in chronic myeloid leukemia patients: A case series

Nilesh Wasekar, Aniket B Mohite, Chandrakala S, Vinod P, Rajesh P, Shailesh B, Farah Jijina

Dr. J C Patel Department of Hematology, KEM Hospital, Mumbai, Maharashtra, India

Correspondence to: Nilesh Wasekar, E-mail: nileshwasekar@gmail.com

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ABSTRACT

Chronic myeloid leukemia (CML) is a myeloproliferative disorder characterized by a reciprocal translocation of long arms of chromosomes 9 and 22 (Philadelphia chromosome). Since the approval of Imatinib in 2001, Dasatinib and Nilotinib have been approved for use in Imatinib resistant or intolerant as well as front line treatment for CML cases. The most common side effects of these kinase inhibitors include myelosuppression, nausea, vomiting, diarrhea, mild skin rash, and QTc prolongation, but serious allergic reactions are rare. Here, we present a case series of Nilotinib induced dermatologic toxicities.

KEY WORDS: Nilotinib; Skin Rash; Chronic Myeloid Leukemia

INTRODUCTION

Nilotinib is a second-generation Bcr-Abl tyrosine kinase inhibitor used for the treatment of chronic myeloid leukemia (CML). Nilotinib has favorable safety profiles but is associated with a number of adverse events (AEs), including rash. The reported incidence of rash in clinical trials varies for Nilotinib ranging from 22% to 62%.^[1-3] However, the term “rash” is non-specific, and the type of rash associated with this agent has not been systematically analyzed.

CASE REPORTS

Case 1


A 50-year-old man, known the case of CML (Imatinib resistant), being treated with Nilotinib 400 mg (Tasigna), twice daily for 4 months, presented with multiple erythematous

scaly plaques over his trunk and extremities for 1 month. The lesions had gradually increased in size and number and spread over the body with mild itching. There was no personal or family history of similar skin lesions. He was not on any other medications and denied any other illness. Examination revealed multiple bilaterally symmetrical, well-defined erythematous plaques of varying sizes with characteristic silvery-white scales over the scalp, trunk, upper limbs, lower limbs, and hands (Figure 1).

Histopathological examination revealed hyperkeratosis, acanthosis, loss of granular layer, supra-papillary thinning, dilated papillary dermal vessels, and a perivascular chronic inflammatory infiltrate in the dermis s/o psoriasis vulgaris (Figure 2). The treatment with topical fluticasone propionate 0.05% and topical calcitriol ointment with 0.5 mg/kg of prednisolone daily for 6 weeks with close monitoring. All the psoriatic lesions are well controlled after treatment. Nilotinib has been continued without any change in the dose or interruption (Figure 3).

Case 2

A 23-year-old male, diagnosed case of CML-chronic phase (CP), started on Nilotinib 300 mg twice daily as first-line treatment. The patient presented after 7 days of starting

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Nilotinib, with milarial skin rash with itching, over the extremities to begin with, then spreading all over body. There was no personal or family history of similar skin lesions. He was not on any other medications and denied any other illness. The patient was given topical emollient and antihistaminic for 7 days and same dose of Nilotinib continued. Patient improved completely and is in complete cytogenetic response (CCYR) at 3 months (Figure 4).

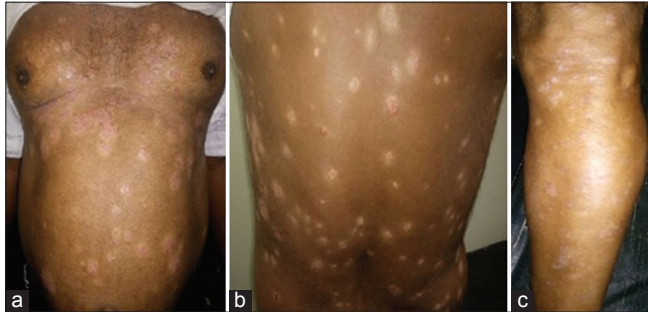


Figure 1: (a-c) Multiple bilaterally symmetrical erythematous plaques of varying sizes with characteristics silvery-white scales over the abdomen, back and lower limbs. Nails and joints were normal

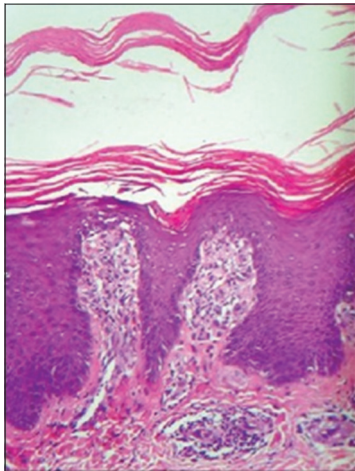


Figure 2: Histopathological examination revealed hyperkeratosis, acanthosis, dilated papillary dermal vessels, loss of granular layer, supra-papillary thinning and a perivascular chronic inflammatory infiltrate in the dermis along with few dermal neutrophils, consistent with psoriasis vulgaris without interface changes, exocytosis of lymphocytes, no eosinophils or plasma cells could be observed in the dermis



Figure 3: (a and b) Skin lesions improved after treatment

Case 3

About 32-year-old female, diagnosed case of CML-CP, started on Imatinib 400 once daily as first-line treatment. Patient was shifted to Nilotinib 400 mg twice daily after 6 months of therapy, in view of Imatinib intolerance. Patient developed maculopapular lesions occurring most prominently on the forearms and trunk after 1 month of treatment with Nilotinib. There was no personal or family history of similar skin lesions. She was not on any other medications and denied any other illness. Patient received topical Calcitriol ointment with topical emollient for 15 days without change in dose of Nilotinib. Patient is asymptomatic at present and completed 2.5 months of Nilotinib.

Case 4

About 33-year-old, diagnosed case of CML-CP, started on Imatinib 400 once daily as first-line treatment. Patient was shifted to Nilotinib 400 mg twice daily after 9 months of therapy, in view of Imatinib intolerance. Patient developed maculopapular lesions occurring most prominently on the forearms, face, and trunk after 15 days of treatment with Nilotinib. There was no personal or family history of similar skin lesions. She was not on any other medications and denied any other illness. Patient received topical Calcitriol ointment with topical emollient for 15 days without change in dose of Nilotinib. Patient is asymptomatic at present and completed 8 months of Nilotinib and in MMR after 6 months of starting Nilotinib.

Case 5

A 45-year-old male, diagnosed case of CML-CP, started on Nilotinib 300 mg twice daily as second line treatment. Patient presented after 7 days of starting Nilotinib, with milarial skin

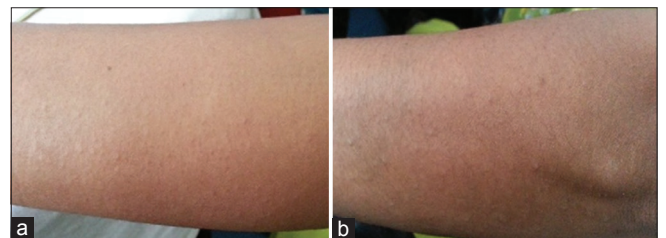


Figure 4: (a and b) Maculo-papular rash after Nilotinib

rash with itching, over the extremities. There was no personal or family history of similar skin lesions. He was not on any other medications and denied any other illness. The patient was given topical emollient and antihistaminic for 14 days and same dose of Nilotinib continued. Patient improved completely and is in CCYR at 3 months.

DISCUSSION

Although Dasatinib and Nilotinib have been available for use in therapy of CML in the second-line settings for several years, new studies have provided the first direct comparison with Imatinib in the first-line setting. In general, Imatinib, Dasatinib, and Nilotinib are associated with broadly similar types of AEs, although the relative occurrence of different AEs varies between agents and some AEs are specific to one drug. For best management of CML patients receiving TKI therapy, knowledge of potential toxicities, how to avoid them, how to deal with them should they arise, and how they may affect response and outcome, are important factors.

In general, BCR-ABL inhibitors are well tolerated (Grades 1 and 2) and result in a limited number of higher-grade toxicities (Grades 3 and 4). Experience with Imatinib in the IRIS trial and with Dasatinib and Nilotinib in the second-line setting suggest that AEs tend to occur early during the course of treatment and late-onset toxicity is uncommon.^[4-6]

Rash is one of the most common non-hematologic AEs.^[7-10] In the IRIS study, rash occurred in 34% although Grade 3-4 rash was infrequent (2%). Pruritus (7%) and alopecia (4%) were also noted in smaller numbers of patients.^[10] In the DASISION trial, first-line Dasatinib treatment resulted in fewer cases of rash compared with Imatinib treatment (11% vs. 17%), with Grade 3-4 rash occurring in 0% versus 1%, respectively. No rates were provided for pruritus or alopecia, suggesting that the frequencies were <10% in both arms.^[4,5]

The pathogenic mechanism of rash in these patients has thus far not been studied.^[8] Given that the majority of tyrosine kinases are active in the skin, their inhibition has a putative role in rash development. Nilotinib inhibits the following kinases, in order of potency: Discoidin domain receptor 1 (DDR1) > DDR-2 > Bcr-Abl > platelet-derived growth factor (PDGF) receptor- α - β > KIT > colony stimulating factor 1 receptor. Nilotinib decreases extracellular matrix protein synthesis in fibroblasts derived from human skin biopsies. It decreased transforming growth factor- β -stimulated collagen production by 50% and PDGF-stimulated collagen production by 51%.^[8]

In the MDACC study, 58% of patients experienced "skin toxicity" with Dasatinib, which was Grade 3-4 in 2%. In addition, 8% experienced pruritus of which 2% was Grade 3-4. Dermatologic toxicity seems to be more common

with Nilotinib than Imatinib.^[11] In the ENESTnd trial, rash occurred in 31% taking Nilotinib 300 mg BID, 36% taking Nilotinib 400 mg BID, and 11% taking Imatinib (Grade 3-4 in <1% vs. 3% vs. 1%, respectively). Pruritus was also more common in both Nilotinib arms (15% with 300 mg BID and 13% with 400 mg BID) compared with Imatinib (5%), as was alopecia (8% with Nilotinib 300 mg BID, 13% with Nilotinib 400 mg BID, and 4% with Imatinib).^[12]

In single-arm trials of first-line Nilotinib 400 mg BID, rash occurred in 49% (2% Grade 3-4) of patients in the MDACC trial^[3] and in 42% (5% Grade 3) in the GIMEMA trial. Pruritus also occurred in 21% of patients in the GIMEMA trial (4% Grade 3).^[1-3]

CONCLUSION

Nilotinib is a newer effective chemotherapeutic agent for the treatment of CML, optimal management of adverse effects requires prompt recognition and collaboration between dermatologists and hematologists.

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