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J Oncol Pharm Pract published online 7 January 2014

DOI: 10.1177/1078155213518226

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Late onset imatinib-induced Stevens–Johnson syndrome

Evan Bois¹, Lisa M Holle² and Umar Farooq³

Abstract

Imatinib, a BCR-ABL tyrosine kinase inhibitor, is known to cause mild to moderate cutaneous reactions in up to approximately 20% of patients. It rarely causes severe reactions, such as Stevens–Johnson syndrome, which can be life threatening. Typically, these rashes occur within two months of initiating therapy. We report a case of Stevens–Johnson syndrome induced by imatinib after several years of therapy, but later successfully was treated with nilotinib therapy.

Keywords

Imatinib, Stevens–Johnson syndrome, rash

Introduction

Imatinib mesylate (Gleevec) is a selective BCR-ABL tyrosine kinase inhibitor.¹ It is an effective treatment for chronic myeloid leukemia (CML).¹ Imatinib has been reported to cause mild to moderate cutaneous eruptions in 7–21% of patients treated with higher doses (400–600 mg/day).¹ Five percent of known cutaneous eruptions secondary to imatinib are severe.² Mild reactions are described as a Grade 1 rash (macular or papular eruption or erythema without associated symptoms), and moderate reactions are described as a Grade 2 rash (macular or papular eruption or erythema with pruritus covering <50% of body surface area).³ Severe reactions are described as a Grade 3 rash (symptomatic generalized erythroderma or macular, papular or vesicular eruption or desquamation covering >50% of body surface area) or Grade 4 rash (generalized exfoliative dermatitis or ulcerative dermatitis) which can be life threatening.³

Stevens–Johnson syndrome (SJS) is a severe, life-threatening adverse cutaneous reaction related to medications with a mortality rate below 5%.⁴ SJS is also frequently used as a synonym for erythema multiforme major, resulting in confusion.⁴ It is rare, occurring 0.01–0.1% of the time. These adverse cutaneous reactions typically occur nine days and two months after starting imatinib at daily doses of 400–600 mg.¹ Herein, we report a case where SJS developed several years

after initiation of imatinib. Subsequently, the patient also developed a skin rash while receiving dasatinib, but later tolerated nilotinib.

Case report

Herein, we present a case of a 22-year-old man with diagnosis of CML. He initially presented with generalized weakness, blurry vision, bilateral flank pain, and weight loss of approximately 20 lb. On physical examination, he had hepatosplenomegaly. His retinal examination showed increased venous caliber and areas of intraretinal hemorrhages. His complete blood count showed a white blood cell count of $540 \times 10^3/\mu\text{L}$, hemoglobin of 11.6 g/dL, and platelets of $141 \times 10^3/\mu\text{L}$. There were 4% blasts in his peripheral blood. His bone marrow biopsy was markedly hypercellular and showed complete replacement of marrow by proliferating granulocytic cell family. His cytogenetics showed

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9;22 translocation. He received leukapheresis and was started on hydroxyurea, intravenous fluids, and allopurinol. After the diagnosis of CML, he was initiated on imatinib 400 mg daily. He achieved major molecular response with this therapy, documented by quantitative polymerase chain reaction (PCR) for BCR-ABL. He had been receiving imatinib for almost six years when he presented to the hospital with five days history of generalized rash. He did report that he had stopped taking imatinib for about six months, and he reinitiated the medication eight months before the development of this rash. It started on his palms and then gradually spread to involve his arms, legs, feet, and trunk. This was preceded by a two-week history of dry non-productive cough. He developed redness and burning sensation in both eyes along with thick discharge. He had painful sores in his mouth and nose. He was unable to eat due to it and required parenteral nutritional support during his hospitalization. He reported history of fever, headache, myalgias, and lower back pain but denied any nausea, vomiting, diarrhea, shortness of breath, or chest pain. It was noted that in addition to imatinib, he was taking ibuprofen as well for his lower back pain. He was not on any other medications.

At initial evaluation, the possibility of imatinib-related rash as well as herpes simplex virus infection was considered as the cause of his rash. His imatinib was discontinued and intravenous acyclovir treatment was initiated. He was found to have a left buttock abscess, which was drained with an incision and he was started on vancomycin. He was treated symptomatically with pain control and hydration. His cultures for viruses or bacteria were negative. A skin lesion from his left forearm was biopsied that showed necrotic keratinocytes within the epidermis with a subepidermal split. A superficial perivascular, predominantly lymphocytic infiltrate, was present in the dermis. There was non-specific trapping of all immunoreactants (IgA, IgM, CC3, and fibrinogen) within the subepidermal colloid body and apparent necrotic epidermis with superficial dermal interstitial fibrinogen deposition. These findings were consistent with SJS. He was diagnosed with imatinib-related SJS. Therefore, the imatinib was not restarted. Throughout his admission, he was also treated with diphenhydramine, hydroxyzine hydrochloride, esomeprazole magnesium, quetiapine, nystatin, aquaphor, fentanyl, docusate, senna, triamcinolone cream, erythromycin eye drops, and enoxaparin. Within two to three weeks, his rash began to improve.

After improvement in his condition and his discharge from the hospital, other treatment options for CML were discussed. While taking in to account the severe life-threatening reaction, we recommended newer anti-tyrosine kinase inhibitors for the treatment

of his CML. Dasatinib, a newer tyrosine kinase inhibitor with a 325-fold increased potency against BCR-ABL kinase, was selected.⁵ He was started on dasatinib 100 mg orally once daily. His medication at this time included fentanyl patch, milk of magnesia, bisacodyl, as needed hydromorphone orally and as needed ibuprofen. Around the same time, he was starting on dasatinib, he was found to have methicillin-resistant *Staphylococcus aureus* infection of skin in his groin. He was prescribed trimethoprim/sulfamethoxazole by his primary care physician. One week later, he was re-evaluated and found to have red, raised, painful skin lesions on his palms. He also reported intermittent episodes of penile vesicles and ulcerations and was evaluated for genital herpes. He was admitted to the hospital for observation and the management of his new rash. We consulted Dermatology, and an extensive work up was done to rule out other causes for the new rash on his palms. He was empirically treated with acyclovir for possible genital herpes. We discontinued both the trimethoprim/sulfamethoxazole and dasatinib and initiated on prednisone 40 mg by mouth daily for five days. He also received diphenhydramine, nystatin suspension, and bactroban cream. It was difficult to determine whether this new rash was secondary to dasatinib versus trimethoprim/sulfamethoxazole versus SJS secondary to herpes infection. He reported previous episodes of genital herpes in past, and he was discharged from the hospital with valacyclovir 1 g by mouth daily with the plan to initiate tyrosine kinase inhibitor therapy once the rash began to subside. He had a biopsy of his penile lesion as an outpatient and it showed findings consistent with lichen planus. Following a complete resolution of his rash, the patient was initiated on nilotinib as an inpatient due to the past reaction with imatinib. He has had an excellent response on nilotinib 300 mg orally twice daily since then, with a major molecular response with PCR for BCR-ABL. No further recurrence of the rash has been found.

Discussion

Although imatinib is one of the most active agents for the treatment of CML, caution must be exercised when skin rashes occur.⁶ Some studies suggest that the inhibition of metabolic pathways mediated by tyrosine kinase, like c-kit, could be involved in the pathophysiology of these skin reactions while other reports suggest a hypersensitivity mechanism.¹ The drug is associated with urticarial, maculopapular exanthema, generalized exanthematous pustulosis, exfoliative dermatitis, and SJS.² Cutaneous reactions to imatinib appear to be related to escalating doses of the drug. Prompt withdrawal of the drug is important when imatinib-induced SJS is of high suspicion.² Managing significant

cutaneous reactions for imatinib can include short-term corticosteroid therapy or reintroducing the drug at a lower dose and slowly escalating it.⁷ This can put the patient at a risk of a poor cytogenetics response. With a Grade 3 or 4 rash, systemic corticosteroid therapy with prednisone 1 mg/kg daily is recommended by some with or without topical triamcinolone acetonide 0.1% ointment for treatment of symptoms.⁸ SJS occurrence requires immediate discontinuation of imatinib with the addition of systemic steroid therapy.⁸ Some patients may be able to be re-challenged with low-dose imatinib (100 mg daily) with a tapering of steroids and closely escalating the dose of imatinib.⁸ Newer second-generation tyrosine kinase inhibitors, such as nilotinib and dasatinib, are considered safe in patients intolerant to imatinib because of a lack of cross-reactivity.^{5,8} After imatinib failure, patients with CML have demonstrated remarkable efficacy when being placed on nilotinib or dasatinib.⁸ Dasatinib unlike nilotinib and imatinib binds BCR-ABL in the active conformation.⁹ Nilotinib like imatinib binds to the inactive BCR-ABL kinase but only requires four hydrogen bonds to stabilize the binding compared to six with imatinib.⁹ It has a 20- to 30-fold higher potency than imatinib against BCR-ABL.⁸ While the incidence of rash in imatinib has been reported up to 40%, it has been found to be between 11% and 27% for dasatinib.¹⁰ Similar results have been shown for nilotinib with Grades 3 and 4 skin rashes <1% while imatinib was 2%–5%. A multivariate analysis showed female sex and the daily dose of imatinib are independent risk factors for the development of an imatinib-induced rash.⁸

Conclusion

SJS is a life-threatening reaction that occasionally occurs with imatinib. Imatinib, along with other tyrosine kinase inhibitors, are also associated with less severe cutaneous reactions. When treating a less severe cutaneous reaction, steroid therapy should be administered and reducing the dose of imatinib is suggested. If SJS occurs with imatinib therapy, immediate discontinuation of imatinib should occur and an alternative tyrosine kinase inhibitor such as dasatinib or nilotinib should be initiated. Although most SJS reactions occur with initiation of therapy, delayed-onset of

SJS is possible. Using the same treatment approach as with early onset SJS seems to be appropriate.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflicts of interest

None declared.

References

1. Hsieh HJ, Chan AL and Lin SJ. Stevens–Johnson syndrome induced by combination of imatinib and allopurinol. *Chemotherapy* 2009; 55: 197–199.
2. Mahapatra M, Mishra P and Kumar R. Imatinib-induced Stevens–Johnson syndrome: recurrence after re-challenge with a lower dose. *Ann Hematol* 2007; 86: 537–538.
3. Valeyrie L, Bastuji-Garin S, Revuz J, et al. Adverse cutaneous reactions to imatinib (STI571) in Philadelphia chromosome-positive leukemias: a prospective study of 54 patients. *J Am Acad Dermatol* 2003; 48: 201–206.
4. Roujeau JC and Stern RS. Severe adverse cutaneous reactions to drugs. *N Engl J Med* 1994; 331: 1272–1285.
5. Wei G, Rafiyath S and Liu D. First-line treatment for chronic myeloid leukemia: dasatinib, nilotinib, or imatinib. *J Hematol Oncol* 2010; 3: 47.
6. Severino G, Chillotti C, Lisa RD, et al. Adverse reactions during imatinib and lansoprazole treatment in gastrointestinal stromal tumors. *Ann Pharmacother* 2005; 39: 162–164.
7. Rule SA, O'Brien SG and Crossman LC. Managing cutaneous reactions to imatinib therapy. *Blood* 2002; 100: 3434–3435.
8. Quintas-Cardama A, Cortes JE and Kantarjian H. Practical management of toxicities associated with tyrosine kinase inhibitors in chronic myeloid leukemia. *Clin Lymphoma Myeloma* 2008; 8(Suppl 3): S82–S88.
9. DeRemer DL, Ustun C and Natarajan K. Nilotinib: a second-generation tyrosine kinase inhibitor for the treatment of chronic myelogenous leukemia. *Clin Ther* 2008; 30: 1956–1975.
10. Huang X, Patel S, Ahmed N, et al. Severe toxicity of skin rash, fever and diarrhea associated with imatinib: case report and review of skin toxicities associated with tyrosine kinase inhibitors. *Drug Des Devel Ther* 2009; 2: 215–219.