Severe Skin Reaction in a Patient with Gastrointestinal Stromal Tumor Treated with Imatinib Mesylate

VIRGINIA FERRARESI¹, CATERINA CATRICALÀ², MARIANGELA CICCARESE¹, ANGELA FERRARI², MASSIMO ZEULI¹ and FRANCESCO COGNETTI¹

¹Department of Medical Oncology A, Regina Elena Cancer Institute, Rome; ²Department of Oncologic Dermatology, San Gallicano Institute, Rome, Italy

Abstract. Imatinib mesylate is a selective protein kinase inhibitor, highly active in patients with chronic myeloid leukemia (CML) and gastrointestinal stromal tumors (GISTs). Cutaneous toxicity, a well-recognized, dose-related side-effect of imatinib mesylate, has been reported in 18 to 69% of patients with GIST treated with doses ranging from 400 to 800 mg once a day. In this case-report a severe skin reaction observed in a patient with GIST treated with imatinib mesylate, in an adjuvant setting and whose severity led to definitive drug discontinuation, is described. Therapeutic management and clinical course are illustrated.

Imatinib mesylate is a tyrosine kinase inhibitor approved for the treatment of chronic myeloid leukemia (CML) and gastrointestinal stromal tumors (GISTs) (1). The most common reported non-hematological side-effects include nausea, vomiting, abdominal pain, edema and weight gain (2).

All grades of cutaneous reactions have been reported in 18 to 69% of patients with GIST treated with a daily imatinib mesylate dose of 400 to 800 mg. These reactions are generally presented in the form of rash with skin dryness and itching and, more rarely, as clinical manifestations ranging from exfoliative dermatitis to vesicular rash and Steven-Johnson syndrome (3-6).

Here the case of a severe skin reaction observed in a patient with GIST, treated with imatinib mesylate, in an adjuvant setting is presented.

Case Report

A 58-year-old caucasian female patient underwent surgical excision of a voluminous abdominal mass, with a resection of stomach, spleen, pancreatic tail, omentum, and a liver nodule, with a histological diagnosis of GIST of gastric origin, with involvement of splenic hilum, peripancreatic tissues and a liver metastasis. The tumor was KIT-positive by CD117 immunohistochemical staining expression. The patient did not suffer from any severe concomitant disease, except for blood hypertension treated with metoprolol tartrate and had no personal history of skin disorders.

A post-surgical total body CT scan and PET did not reveal persistence or distant sites of disease but, in consideration of the tumor extension, it was decided to treat the patient with a daily imatinib mesylate dose of 400 mg, in an adjuvant setting.

Two months after beginning the treatment, the patient developed an erythema, covered by white thin and dry scales localized on the forearms and hands; a mild periorbital edema also occurred. Systemic antihistamines were administered to the patient to control itching without suspension of imatinib mesylate, which was reduced to 300 mg once a day. However, one month later, a progressive worsening of the cutaneous clinical aspect characterized by an extension of erythema and scales on the upper and lower limbs (Figure 1A, B) was observed. The infected skin appeared moist and exudative and oedema of the lower limbs also occurred. Both palms were covered with erythema, hyperkeratosis and scaling. These clinical findings were compatible with the diagnosis of an exfoliative dermatitis or erythroderma. A skin biopsy was not performed, due to the potential risk of the wound not being able to heal. The patient also reported an associated deep sensation of fatigue, with lack of appetite and depression.

The treatment was promptly discontinued and the patient was treated with systemic steroids (oral prednisone, 25 mg daily), diuretics and local application of emollient creams.
One week after the suspension of the drug, an improvement of cutaneous manifestations was evident with a reduction of the extension and severity of erythema, exudates and scales.

Further clinical dermatological controls performed fifteen days and two months later, revealed a progressive improvement until the lesions were disappeared, leading to the occurrence of hyperpigmented areas. However, considering the «adjuvant» intent of the treatment, the severity of the toxicity and the patient’s request, the therapy with imatinib mesylate was stopped completely.

Discussion

Cutaneous toxicity is a well-recognized side-effect related to imatinib mesylate administration. The data on the cutaneous toxicity related to imatinib administration in patients with GISTs (and other subtypes of soft tissue sarcomas), treated in the context of controlled clinical trials, are summarized in Table I.

In most cases, the dermatological toxicity was mild to moderate and not dose-limiting, severe events being reported in 2 to 15% of patients, depending on the series.

As for CML patients, the incidence of skin reactions in GISTs patients was, in generally, dose-dependent with a total rate of occurrence as high as about 40-70% for patients receiving the higher dose (600-800 mg once a day).

In the study by Verweij et al. (6), comparing a daily imatinib mesylate dose of 400 mg versus twice daily in patients with advanced GIST, cutaneous toxicity occurred in 125 out of 470 patients (26.6%) versus 220 out of 472 patients (46.6%), treated with the lower versus the higher dose, respectively and the difference was statistically significant (adjusted $p$ value according to the Hommel step-up procedure: $<0.0001$) (6). The incidence of severe dermatological toxicity was quite low, being reported by 2.3% and 5.3% of patients treated with doses of 400 and 800 mg, respectively. In the same clinical trial, the cross-over from the low dose (400 mg daily) to the high dose (800 mg daily) of the drug upon progression was no more likely to be associated with increased cutaneous toxicity (7). This phenomena may, however, be explained by the increase in drug clearance over time, which leads to a reduction in exposure, thereby masking the dose-effect of the drug on toxicity (8).

The dose-related skin toxicity demonstrates a pharmacological effect of imatinib mesylate, even if the occurrence of skin reactions with a low dose of the drug (400 mg once a day) might indicate the existence of hypersensitivity.

In most cases, cutaneous manifestations consist of a self-limiting erythema associated or not with itching and skin dryness, commonly tending to decrease in severity over time, in spite of continued treatment.

In some patients, cutaneous clinical manifestations may be severe and characterized by macular or papular rash, photosensitivity, palpable purpura, hypotricosis, hypo-/hyper-pigmentation of the skin, psoriasis, bullous eruptions and, rarely, angioedema, vesicular rash and Steven-Johnson syndrome.
Several case-reports, the majority of which concern patients with CML, noted the occurrence of dose-limiting skin disorders during imatinib administration (9-13).

Therapeutic management of skin reactions consists, in general, of the use of low doses of corticosteroids without drug suspension (or with a temporary dose-reduction) in the case of mild to moderate toxicity. In the event of severe skin reaction, a transient discontinuation of imatinib mesylate and a systemic corticosteroid treatment may be required. Furthermore, depending on individual cases, a gradual re-introduction of the drug may be attempted. Only in a few cases does the severity of the skin reaction require a definitive interruption of imatinib administration.

Concerning the pathogenesis of skin reactions occurring during imatinib administration, a direct effect of the tyrosin-kinase inhibition on PDGF receptor, expressed on dermal mast cells and on blood vessels, was suggested (13, 14). The inhibition of this receptor might induce an increase of dermal interstitial fluid pressure with a subsequent phenomena of skin edema, erythema and desquamation (14). However, the histological evidence of an increased number of dermal mast cells, which express a functional c-kit receptor, in cases of severe skin toxicity from imatinib mesylate, seems to exclude a direct effect of the drug on mast cells themselves (9, 15). As a result, it has also been suggested that imatinib mesylate might act as a dose-dependent inducer of chemoattractant substances (e.g., cytokines and growth factors), able to induce dermal mast cell accumulation (9).

In our case, the severity of the reaction which had not improved after the dose reduction of imatinib, along with the bad general condition of the patients led us to discontinue the "adjuvant" treatment. The time of occurrence (>8 weeks from imatinib therapy initiation), the dermatological aspect and the modalities of clinical presentation seem to support the hypothesis of a pharmacological effect, also considering the concomitant occurrence of other typical imatinib-related side-effects (i.e. edema).

In conclusion, according to the data reported in literature, our experience with GIST patients treated with daily imatinib mesylate doses ranging from 400 to 800 mg, confirms a reasonable tolerability of the drug. In particular, severe skin toxicity is a very rare adverse event, the management of which requires adequate supportive care, as well as a careful evaluation of temporary or definitive modifications of the dose of imatinib mesylate.

References


Table I. Cutaneous toxicity (National Cancer Institute Common Toxicity Criteria) during imatinib administration in patients with GISTs and other soft tissue sarcomas.

<table>
<thead>
<tr>
<th>Publication</th>
<th>Phase</th>
<th>Dose (mg/d)</th>
<th>No. of patients</th>
<th>% All grades (pts)</th>
<th>%Grade 3-4(pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>van Oosterom et al.</td>
<td>I</td>
<td>400</td>
<td>8</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>600</td>
<td>8</td>
<td>55 (22)</td>
<td>12.5 (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>800</td>
<td>16</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1,000</td>
<td>8</td>
<td>12.5 (1)</td>
<td>-</td>
</tr>
<tr>
<td>Demetri et al.</td>
<td>II randomized</td>
<td>400</td>
<td>73</td>
<td>24.7 (18)</td>
<td>2.7 (2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>600</td>
<td>74</td>
<td>36.5 (27)</td>
<td>2.7 (2)</td>
</tr>
<tr>
<td>Verweij et al.</td>
<td>II</td>
<td>800</td>
<td>51</td>
<td>69 (35)</td>
<td>14 (7)</td>
</tr>
<tr>
<td>Verweij et al.</td>
<td>III</td>
<td>400</td>
<td>470</td>
<td>26.6 (125)</td>
<td>2.3 (11)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>800</td>
<td>472</td>
<td>46.6 (120)</td>
<td>5.3 (25)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>1,180</td>
<td>37.9 (447)</td>
<td>4.1 (49)</td>
</tr>
</tbody>
</table>


Received June 26, 2006
Accepted September 14, 2006