Stevens-Johnson Syndrome Induced by Masitinib

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Masitinib mesylate (AB1010) is a novel tyrosine kinase inhibitor (TKI) that is a potent inhibitor of wild-type c-kit, its activated mutated form in the juxtamembrane region, platelet-derived growth factor receptors alpha and beta, fibroblast growth factor receptor 3, and the focal adhesion kinase activation pathway. It has greater affinity for the c-kit receptor than do other TKIs (e.g. imatinib), suggesting greater safety (1).

It has been suggested to be an effective treatment for advanced gastrointestinal stromal tumours (2), advanced pancreatic cancer (3), cutaneous mastocytosis (4), rheumatoid arthritis (5), and severe asthma (6). It is currently being evaluated in three phase III studies: i.e. in patients with non-resectable or metastatic stage 3 or stage 4 melanoma with a mutation in the juxtamembrane domain of c-kit in comparison with dacarbazine; in patients with gastro-intestinal stromal tumours in comparison with imatinib; and in comparison with placebo in the treatment of patients with systemic or cutaneous handicapping mastocytosis.

We report here the first case of Stevens-Johnson syndrome (SJS) induced by masitinib.

CASE REPORT

A 55-year-old man, with no previous medical history, was referred for a rash. He had adenocarcinoma of the colon with bone, pulmonary and hepatic metastases, previously treated with first-line chemotherapy (six cycles of fluorouracil and folinic acid plus irinotecan and bevacizumab) that had been withdrawn 2 months before because it was ineffective. The patient had then been included in a phase I/II open trial evaluating masitinib in combination with second-line chemotherapy (in his case: fluorouracil and folinic acid plus oxaliplatin, FOLFOX). One infusion of FOLFOX had been administered 27 days before the rash, and ondansetron, metoclopramide and macrogol had been introduced in the meantime. Masitinib (9 mg/kg/day orally) was started 12 days before the rash, along with cetirizine and oxycodone. Moreover, he had been receiving long-term treatment with zolpidem.

At clinical examination, he presented with fever, deterioration of his general condition, asthenia, maculopapular exanthema on the trunk and proximal parts of the limbs (Fig. 1) and erosive cheilitis (Fig. 2). The erythema spread rapidly to 80% of the body surface, with blistering on 5% of the skin surface, associated

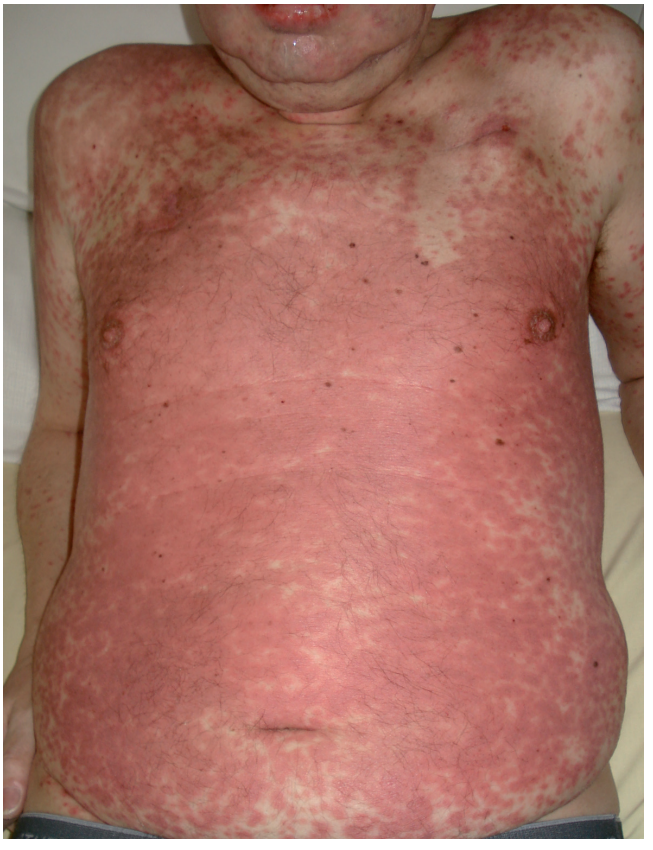

Fig. 1. Maculopapular exanthema of the trunk and proximal parts of the limbs 12 days after masitinib ingestion.

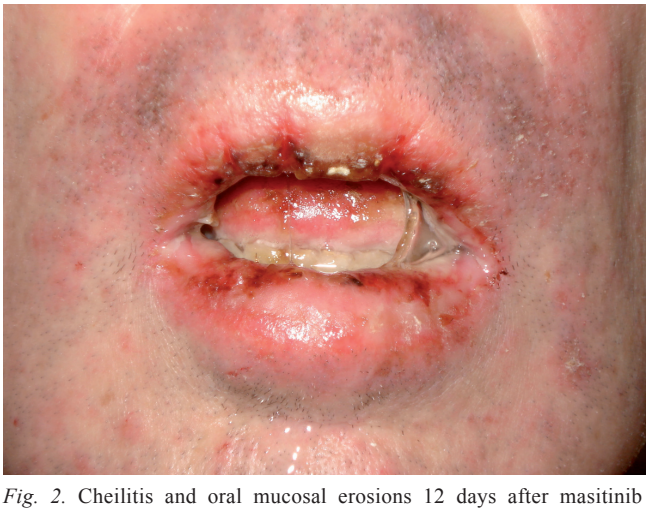

Fig. 2. Cheilitis and oral mucosal erosions 12 days after masitinib ingestion.

with erosions on the oral, conjunctival and genital mucosae.

Skin biopsy showed massive necrosis of the epidermis, with oedema and a lymphohistiocytic inflammatory infiltrate in the superficial dermis. These findings were consistent with SJS.

Masitinib, cetirizine, oxycodone and metoclopramide were stopped, and oxaliplatin was not re-administered. Zolpidem and macrogol were continued. Cutaneous and mucosal lesions improved rapidly with symptomatic treatment (topical steroids and nutritional support) and resolved completely after 4 weeks.

Fluorouracil, folinic acid, oxycodone and ondansetron were later re-administered with no recurrence of skin symptoms.

DISCUSSION

In this case, there was strong evidence for SJS induced by masitinib. We considered the causative role of all medication introduced from 4 to 28 days before the rash (masitinib, cetirizine, metoclopramide and oxaliplatin, excluding those which had been continued or re-administered safely afterwards). To our knowledge, there has been no report of toxic epidermal necrosis or SJS with metoclopramide (used since the 1960s), cetirizine or oxaliplatin (used since the mid-1980s).

In previous studies evaluating masitinib the adverse events reported have ranged from 84% to 100% (2–6), the most frequent being gastro-intestinal, haematological and cutaneous side-effects. The main cutaneous side-effects reported were rash (28–50%) (2–6), peripheral oedema (18.2–40.9%) (2, 3, 6), pruritus (33%) (2), mucosal inflammation (16.9–18.2%) (2, 3) and dry skin (13.3%) (2). Eczema (4, 5), aphthous stomatitis (4, 5), gingivitis (4), dermatitis psoriasiform (4), dry mouth (5), alopecia (5), petechia (5), onychoclasis (5), photosensitivity reaction (5) and skin exfoliation (2) were also reported occasionally. No cases of toxic epidermal necrosis (TEN) or SJS were reported. Nevertheless, one case of SJS was reported one week after administration of another tyrosine kinase inhibitor, imatinib (7), which could suggest a class effect.

To our knowledge, this is the first case of SJS induced by masitinib, and practitioners using or evaluating masitinib should be aware of the potential risk of SJS.

ACKNOWLEDGEMENTS

Conflicts of interest: L. Machet and M. Samimi are currently investigators for a phase III clinical trial (AB08026) promoted by AB SCIENCE evaluating masitinib for treatment of stage III/IV melanoma.

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