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New Drug and Possible New Toxicity – Squamous Cell Carcinoma Following Imatinib in Patients with Gastrointestinal Stromal Tumors

FAISAL INAYAT[1] and MUHAMMAD WASIF SAIF[2]

[1]*Department of Medicine, New York-Presbyterian Hospital, Weill Cornell Medical College, New York, NY, U.S.A.;*
[2]*Department of Hematology/Oncology, Tufts Medical Center, Tufts University School of Medicine, Boston, MA, U.S.A.*

Abstract. *Background: Molecularly targeted therapy has revolutionized the treatment of advanced gastrointestinal stromal tumors (GISTs). Specifically, the consistent dependence of GISTs on proto-oncogene c-KIT signaling led to the development and successful implementation of imatinib, a small-molecule c-KIT inhibitor. Imatinib induces, rapid and sustained clinical benefit by blocking the signaling via c-KIT. The most frequently reported adverse reactions (>30%) include edema, nausea, vomiting, muscle cramps, musculoskeletal pain, diarrhea, rash, fatigue and abdominal pain. Case Series: Herein, we report a case series of cutaneous squamous cell carcinoma (SCC) occurring secondary to imatinib in two patients treated for GISTs. Both patients were successfully managed with surgical resection of SCC and the discontinuation of the drug. Furthermore, we undertook a comprehensive literature review on this association. Few cases of cutaneous SCC secondary to imatinib therapy were reported in patients with chronic myeloid leukemia. However, there was no clinical evidence on causation of imatinib-associated SCC in patients with GIST. Conclusion: To our knowledge, the present report is the first to describe imatinib-related SCC in patients undergoing treatment for GISTs. This implicates that safety and long-term tolerability of imatinib in patients with GISTs warrant rigorous testing and close monitoring.*

Gastrointestinal stromal tumors (GISTs) are rare tumors of the gastrointestinal tract characterized by cell-surface expression of the proto-oncogene c-KIT. Imatinib mesylate is a potent and selective tyrosine kinase inhibitor of breakpoint cluster region–Abelson (BCR–ABL) gene, c-KIT, and platelet-derived growth factor receptor A (PDGFRA). It is a first-line standard therapy for inoperable, metastatic, or recurrent KIT-positive GIST and for the adjuvant treatment of patients following resection of primary KIT-positive GIST (1).

After the clinical introduction of imatinib, the therapeutic strategy for GISTs dramatically changed. Imatinib has become one of the hallmarks of targeted therapy developments in oncology. It has dramatically improved the patient outcomes for GIST, with impact on both quality of life and long-term prognosis (2).

The toxicity profile of imatinib has been well characterized. Although the majority of patients experience an adverse event during treatment with imatinib, these side-effects are usually mild and manageable, with the majority of patients continuing treatment uninterruptedly (3). However, the present report highlights an unusual and serious adverse effect of imatinib in patients with GISTs in the form of cutaneous squamous cell carcinoma (SCC).

Imatinib induced-SCC has been reported in patients with chronic myeloid leukemia (4, 5). However, the present study represents the first report highlighting SCC following imatinib in patients with GIST. It prompts that clinicians should maintain a high index of suspicion for SCC in such patients.

Case Series

Case Report 1. The first patient case is of a 90-year-old woman who initially presented to the hospital after routine laboratory studies for anemia. Upper gastrointestinal endoscopy showed 4×5 cm mass with central cavitation. Endoscopic ultrasound (EUS) revealed a mass in the cardia which measured 32 mm in the long axis and 17 mm in luminal diameter. Computed tomography of the chest showed a large hiatal hernia with marked thickening of the distal esophagus. There was an 11 mm enlarged lymph node adjacent to the gastroesophageal junction below the diaphragm, which was suspicious for lymph

Correspondence to: Professor M. Wasif Saif, MD, MB, BS, Director, GI Oncology Program; Leader, Experimental Therapeutics, Tufts University School of Medicine, Tufts Medical Center, South Building, 8th Floor; 800 Washington St., Box 245. Boston, MA 02111, U.S.A. Tel: +1 6176366227, Fax: +1 6176368538, e-mail: WSaif@tuftsmedicalcenter.org

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Table I. *Cases of squamous cell carcinoma following imatinib therapy reported in literature.*

Case no.	Age (years)	Gender	Diagnosis	Dose of imatinib (mg/day)	Time from start of imatinib to SCC	Other possible etiologies/ risk factor for SCC, except sun exposure	Outcome/ treatment	Reference
1	72	M	CML	600	15 Months	Hydroxyurea administration	Successful resection and irradiation	4
2	73	M	CML	600	2 Years	Hydroxyurea administration	Successful resection	4
3	70	M	CML	300	6 Years	None	Successful resection	5
4	90	F	GIST	400	2 Years	None	Successful resection	Present case series
5	61	F	GIST	400	1 Year	None	Successful resection	Present case series

CML, Chronic myeloid leukemia; GIST, gastrointestinal stromal tumor; SCC, squamous cell carcinoma; M, male; F, female.

node metastasis. Pathology reports of the lesion were positive for c-KIT and negative for S100, smooth muscle actin and desmin, compatible with GIST. No mitotic activity or tumor necrosis was identified in that limited biopsy sample. She was transfused with 1 unit of packed red blood cells and given 200 mg intravenous iron sucrose prior to discharge.

The patient had been administered 400 mg/day imatinib mesylate (Gleevec®, Novartis) for her GIST for 2 years. While her GIST was well-controlled, a small superficial mass emerged on her left anterior shoulder (Figure 1A). It rapidly developed into a 3-cm, ulcerated, reddish nodule with an erythematous halo within 1 month (Figure 1B). Excisional biopsy was performed and the specimen was sent for histopathologic analysis (Figure 1C). Histopathology showed dermal lobules of moderately atypical squamous cells with frequent mitoses and small focal areas of keratinization. There were areas with glandular differentiation and mucin deposition highlighted with Mucicarmine stain.

Computed tomography appeared grossly unchanged, with no metastatic disease, swollen lymph nodes or visceral involvements. Immunohistochemistry showed that tumor cells were strongly positive for p63 and cytokeratin 7. The clinical and histopathological findings led to the diagnosis of SCC with moderate to poor glandular differentiation. Additional resection with 2-cm margin from the postoperative scar was performed.

Following the initial excision of SCC in our patient, three more suspicious growths appeared on her arms and back. Her dermatological surgeon biopsied the lesions and histopathologic evaluation confirmed the diagnosis of SCC. Imatinib was stopped due to the accelerated growth of SCC in this patient. Uneventful excisions of all the SCC lesions were performed and the patient has been regularly followed-up for her GIST and SCC.

Case Report 2. The second case involves a 61-year-old woman, with past medical history remarkable for rheumatoid arthritis, who presented to our institution with a rash 2 cm from the anal verge. Upon further questioning, the patient reported that she had experienced leakage of a small amount of stool and also passing of a small amount of bright red blood in her stool over the past many months. On physical examination, a palpable mass was present just proximal to the anal verge. Imaging and a rectal EUS with fine-needle aspiration biopsies were obtained and pathology was consistent with rectal GIST.

The patient underwent neoadjuvant treatment with 400 mg/day imatinib (Gleevec®, Novartis), followed by a successful rectal resection of the tumor. After 1 year, the patient underwent a follow-up examination and post-surgical imaging was ordered. This showed possible residual disease. Therefore, it was decided to restart imatinib postoperatively on a dose of 400 mg daily.

On 4 months of imatinib therapy, the patient developed mouth sores, worsening fatigue and appetite, as well as facial swelling, thought to be due to imatinib. The medication was reduced to 200 mg daily due to these side-effects.

On 9 months of imatinib therapy, the patient developed ill-marginated, erythematous, rough papule following imatinib on both of her legs (calves) (Figure 2). Skin biopsy of one of the lesions showed aggregates of pleomorphic keratinocytes with nuclear atypia, hyperkeratosis and dyskeratosis in the epidermis. These lesions were consistent with actinic keratosis, which is widely accepted as a precursor to SCC formation.

On 1 year of imatinib treatment, the cutaneous lesion in our patient had progressed to SCC. Imatinib was discontinued immediately and the SCC was managed successfully with surgical resection. However, unfortunately, we were unable to collect the complete data regarding SCC of this patient.

Discussion

The worldwide incidence and prevalence of GISTs are estimated to be approximately 1 to 1.5 per 100,000 per year and 13 per 100,000, respectively (1). Most (50-80%) GISTs arise from a mutation in the c-KIT gene, which encodes a receptor for a growth factor termed stem cell factor (CD117). The c-KIT product is expressed on the interstitial cells of Cajal and a large number of other cells (*e.g.* bone marrow cells, mast cells, melanocytes). Mutations permit c-KIT to function

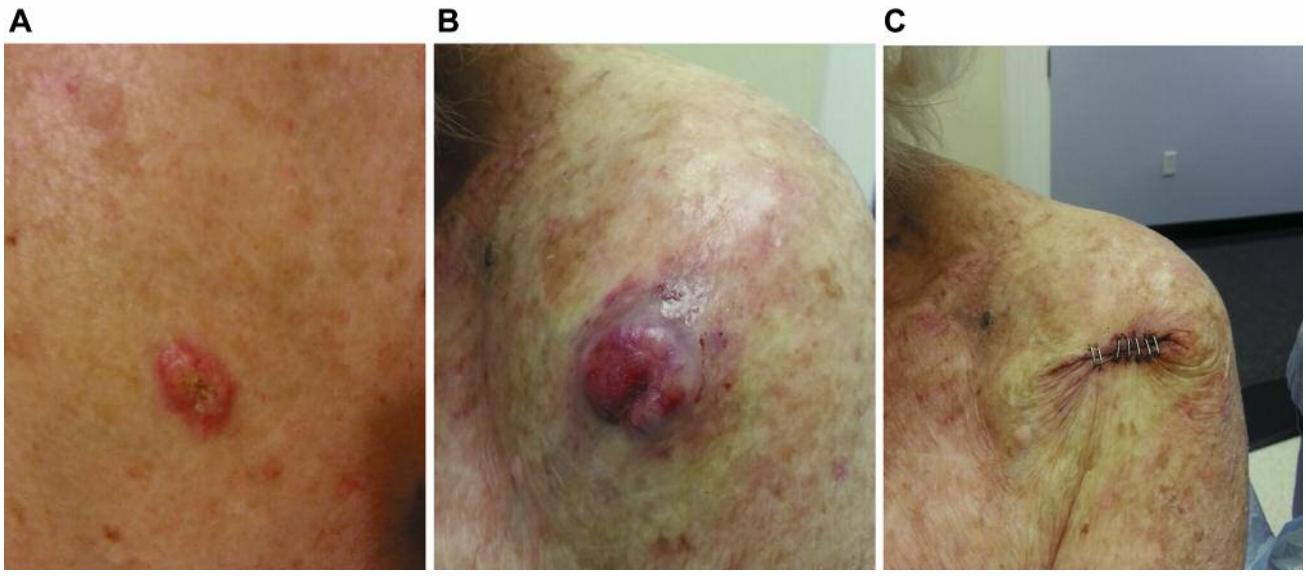

Figure 1. *Case 1. A: Initial small superficial mass on left anterior shoulder following imatinib. B: Progression to a 3-cm, ulcerated, reddish nodule with an erythematous halo. C: Excisional biopsy was performed and the specimen was sent for histopathological analysis, which revealed moderately atypical squamous cells with frequent mitoses and small focal areas of keratinization, areas with glandular differentiation and mucin deposition highlighted with Mucicarmine stain.*

independent of CD117 activation, which leads to a high rate of cell division and genomic instability. It is likely that more mutations are needed for a cell with a c-KIT mutation to develop into a GIST, but the c-KIT mutation is probably the first step of this process (2). In GISTs, imatinib acts through inhibition of the c-KIT pathway, rather than tyrosine kinase inhibition, as in chronic myeloid leukemia (3-5).

Imatinib typically has mild to moderate adverse events that are usually managed without permanent cessation of the drug in patients with GISTs (6). In literature, the most commonly reported side-effects included edema (74%), nausea (52%), diarrhea (45%), myalgia (40%), fatigue (35%), skin rash (30%), headache (30%), abdominal pain (26%), and, rarely, serious gastrointestinal bleeding (2). Another study showed that imatinib was well-tolerated over a long duration with no serious adverse effects (7). In one report on the incidence and frequencies of adverse events in adjuvant randomized trials with imatinib, 30% patients developed serious adverse reactions (8).

Among patients with GISTs who undergo treatment with imatinib, around 30-44% exhibit cutaneous adverse reactions. These skin lesions usually arise early in the treatment and are mostly dose-dependent (9, 10). Erythematous and maculopapular pruritic rash, appearing predominantly on the forearms and trunk are the most frequently reported skin reactions with imatinib. The rash is typically mild, often self-limiting, and managed conservatively, without the need of imatinib discontinuation. However, 2-3% of the cases may develop serious cutaneous reactions requiring the immediate cessation of imatinib therapy. In such cases, oral glucocorticoid may also be administered and tapered off followed by gradual restart of imatinib therapy (11, 12). Erythema multiform and Stevens–Johnson syndrome in patients with chronic myeloid leukemia has also been reported, which resolved after imatinib discontinuation and appropriate treatment (13, 14).

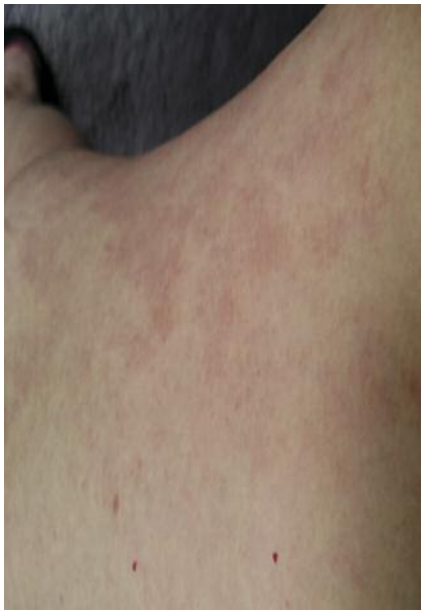

Figure 2. *Case 2, multiple ill-marginated, erythematous rough papules following imatinib, on both calves.*

Previously, there have been reports of patients with chronic myeloid leukemia who developed SCC due to imatinib therapy (4, 5) (Table I). However, SCC in patients with GISTs undergoing treatment with imatinib has never been described in the literature. SCC is the most common type of cutaneous cancer after basal cell carcinoma. It typically appears as a papule or nodule, with varying degrees of hyperkeratosis and ulceration, which arises on sun-exposed skin areas of elderly patients. The incidence of this neoplasm among Caucasians is 100-150 per 100,000 persons each year, and the age-specific incidence among persons over the age of 75 years is approximately 10-times that rate (15).

The most common etiological factor behind SCC is ultraviolet radiation. Such radiation frequently produces point mutations in double-stranded DNA, resulting in the formation of thymidine dimers in the p53 tumor-suppressor gene. Failure of repair mechanisms may then lead to tumor formation. Furthermore, SCC has also been associated with immuno-suppression, arsenic exposure, radiation, chronic ulceration, and human papillomavirus infection. The specific pathogenesis of cutaneous reactions secondary to imatinib is yet to be determined; however, its high prevalence and dose-dependency suggest that these reactions are possibly mediated by KIT and PDGFRA inhibition in dermal and epidermal cells (10, 11, 16). Further studies are warranted in this regard.

Conclusion

While cutaneous SCC usually responds well to surgical intervention, it has the potential to recur locally and even metastasize, leading to significant morbidity and mortality (17-19). Therefore, close monitoring of patients with GISTs undergoing therapy with imatinib is of paramount importance in order to diagnose such severe reactions early and institute effective treatment.

Funding and Conflicts of Interest

The Authors report no biomedical financial interests or potential conflicts of interest in regard to this article.

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