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Cutaneous adverse effects of imatinib mesylate in phototype VI patients treated for chronic myeloid leukemia: Experience from Dakar, Senegal about 60 patients

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Abstract
Imatinib mesylate is a tyrosine kinase inhibitor (TKI) that targets BCR-ABL, c-kit, and PDGF receptors. It is a first line treatment in chronic myeloid leukemia in Senegal, while second line treatments are expensive in our practice. Adverse skin effects are generally well tolerated and the most common are edema, maculopapular rash or diverse eruptions (lichenoid eruptions, Steven-Johnson syndrome, hyperpigmentation and hypopigmentation).
Objectives: Our aim was to identify the cutaneous side effects in phototype VI Senegalese patients who received Imatinib mesylate for the treatment of chronic myeloid leukemia.
Methodology: We performed a descriptive study in population with dark complexion. The study was conducted in the Hematology unit of National Center of transfusion, in Dakar, Senegal. We included the patients who received imatinib mesylate (IM) for chronic myeloid leukemia from January 2008 to December 2017. We excluded those treated for another affection by IM. Socio-demographic, clinical, biological and therapeutic data were recorded by a structured questionnaire. We analysed data by software CS Pro 7.0 and to Stata 12.0 by EPi-info version. The Pearson Chi square test and the Fischer bilateral exact test were used to compare frequencies. If $p<0.05$, the difference was considered statistically significant.
Results: We collected data from 60 patients treated with imatinib mesylate during approximatively 39 months. Among them 55% (n=33) developed cutaneous side effects. The sex ratio was 0.94 (16 males/ 17 females) and the median age of entire cohort was 46,7 years. Fifty-two patients received a daily dosage of 400 mg, and 8 received a 600mg daily dosage. The median time to onset of cutaneous disease was 3, 73 months.
The following adverse cutaneous effects were found: generalized hypopigmentation (n=21), localized hypopigmentation (n=2), periorbital edema (n=4), Stevens-Johnson syndrome (n=3), eczematous dermatitis (n=3), cutaneous dermatophytosis (n=2), hyperpigmentation (n=2), alopecia(n=2), fixed pigmented eruption (n=1), onychodystrophy (n=1), folliculitis(n=1), stomatitis(n=1) and lichenoid reaction(n=1). Extra-dermatological toxicity was observed in 23 patients (38.33%). Skin side effects were mostly associated with gastrointestinal (n=16) and hematologic (n=14) side effects. We found no difference between age, sex and the apparition of cutaneous side effects but it was an association between the dose of the imatinib mesylate (p=0,027) and the stage of the disease ((p=0,047).
Conclusion: cutaneous side effects of Imatinib mesylate are common among patients among the patients followed for chronic myeloid leukemia. Hypopigmentation was the most frequent; we found an association between cutaneous side effects and the dose of Imatinib mesylate.

Keywords: Imatinib mesylate, skin toxicity, chronic myeloid leukemia, phototype VI

Introduction
Imatinib mesylate (IM) is a first generation tyrosine kinase inhibitor (TKI) that targets BCR-ABL, c-kit and PDGF receptors. It is a first line treatment in chronic myeloid leukemia in Senegal, while second line treatments are expensive in our practice.
Chemotherapeutic agents have significant side effects. Adverse skin effects are generally well tolerated and the most common are edema, maculopapular rash or diverse eruptions (lichenoid eruptions, Steven-Johnson syndrome, hyperpigmentation and hypopigmentation).

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Our aim was to identify the cutaneous side effects in phototype VI senegalese patients who received Imatinib mesylate for the treatment of chronic myeloid leukemia.
We perform a descriptive study in population with dark complexion. The study was conducted in the Hematology unit of the National Center of transfusion, in Dakar, Senegal.

Materials and Methods

We have collected data from the Hematology unit of the National Center of transfusion, in Dakar, Senegal of 60 patients treated with Imatinib mesylate during approximatively 39 months. We included the patients who received imatinib mesylate (IM) for chronic myeloid leukemia from January 2008 to December 2017. We excluded those treated for another affection by IM. We started data collection after obtaining consent from the patients. Socio-demographic, clinical, biological and therapeutic data were recorded by a structured questionnaire. We analysed data by software CS Pro 7.0 and to Stata 12.0 by EPi-info version. The Pearson Chi square test and the Fischer bilateral exact test were used to compare frequencies. If $p<0.05$, the difference was considered statistically significant.

Results

Among our patients, 55% (n=33) developed cutaneous side effects. The sex ratio was 0.94 (16 males/ 17 females) and the median age of entire cohort was 46,7 years. Fifty-two patients received a daily dosage of 400 mg, and eight of 600 mg. The median time to onset of cutaneous disease was 3,73 months.
The following adverse cutaneous effects were found (Table 1): 21 patients with generalized hypopigmentation (figure 1), 4 with periorbital edema (figure 2), 3 with Stevens-Johnson syndrome, 3 with eczematous dermatitis, 2 with cutaneous mycosis (figure 3), 2 with hyperpigmentation, 2 with localized hypopigmentation, 2 with alopecia, 1 with fixed pigmented eruption, 1 with onychodystrophy, 1 with folliculitis, 1 with stomatitis, 1 with lichenoid reaction.
We noticed an association of two or more diseases in the same patient such as generalized hypopigmentation, frontal hyperpigmentation, alopecia and eczematous dermatitis (figure 4), hypopigmentation, onychodystrophy, alopecia, cutaneous mycosis and periorbital edema in a patient with artificial depigmentation prior to imatinib therapy, hypopigmentation and folliculitis, hypopigmentation and periorbital edema, also hypopigmentation, eczematous dermatitis and cutaneous mycosis.
The adverse side effects were treated with appropriated drugs. Topical steroids (betamethasone: Diprosone® 1 application at night) have been used to treat eczematous dermatitis and lichenoid eruption. Oral corticosteroids (prednisone 1mg/kg daily) have been used in the Stevens-Johnson Syndroms. Antibiotics in surinfected lesions and folliculitis, antihistaminics and antifungals were needed for extended cutaneous mycosis (Ciclopirox 1%: Mycoster® cream, 1 application twice daily associated with terbinafine 250 mg twice daily). Emollients and sunscreen were prescribed to all patients.
Adverse skin effects were associated mostly with hematologic and gastrointestinal side effects. Patients' age and sex seem not to have any influence on side skin effects, but it was correlated to the dose of treatment. Another finding of the study is the correlation between overall hematologic side effects and skin side effects (p=0,043). However, there is no correlation when each of hematologic side effects is considered individually.
Imatinib mesylate therapy has been temporally suspended in the 3 cases of Stevens-Johnson and reintroduced at a lower dosage associated with oral steroids. Two patients with hypopigmentation stopped voluntarily IM, and skin repigmentation was noticed. None of the other affections needed drug interruption, and they disappeared with treatment, except for the pigmentary disorders.

Discussion

Our study had some limitations. All the diagnostics were not performed by a dermatologist. Pigmentary disorders could not be evaluated properly because of artificial depigmentation of patients prior to imatinib therapy. Lastly, clinical records used as data base did not contain all the information about toxicity prior to the study.
Imatinib mesylate improve prognosis and global survival of patients suffering from CML [1]. During our study time, we collected data about 60 patients treated with imatinib. The median time of treatment was 39 months. The median age of entire cohort was 46,7 years. Fifty-two patients received a daily dosage of 400 mg daily, and 8 received a 600mg daily dosage. Among them, 33 (55%, 16 males; 17 females) developed cutaneous side effects higher than 25% found in Paolino's study [3].
It's a well-tolerated treatment and the skin reactions are mostly mild and moderate [4]. In our study, 40% of adverse skin effects were grade 1 on the CTCAE [5], 53% were grade 2. However, 3 patients (7%) with Stevens-johnson syndrome had grade 3 side effects. Some authors described other severe skin reactions such as, acute generalized exanthematous pustulosis, toxic epidermal necrolysis, DRESS syndrome [6, 7].
Hypopigmentation was the most common adverse skin effects of imatinib in our study (69,7%). An incidence close to that is found in many studies conducted in India: Arora *et al*. [8] 40, 9%, Amitay-Laish *et al*, [9] 41%, Sunita *et al*. [10] 80%, Sharma *et al*. [11] 84%. On the opposite, Paolino's study [3] found no pigmentary disorders if not melanonychia. Hypopigmentation is presented as a hypochromic area most of the time more frequent in dark skin populations [8, 12]. On the other hand, hyperpigmentation is a rare adverse skin effect of IM. Rehman *et al*. [13] reported a case of extensive skin hyperpigmentation and found only two cases of cutaneous hyperpigmentation while reviewing the literature. In our study, hyperpigmentation is only present in two patients. Like Valeyrie *et al*. [4], we documented an association between hypopigmentation and hyperpigmentation in the same patient (figure 4). It seems to be reversible with imatinib discontinuation [10, 11] and could be an indication of non-adherence to treatment.
Edema is the most common side effects described in most studies [1, 3, 14, 15], Valeyrie *et al*. [4] reported a frequency from 63 to 84%. It is superficial, most of the time periorbital, but can also appear as pericardic or pleural effusion. In a study conducted by Ekinci *et al*. [16] in Turkey, 10, 1% of CML patients treated with IM had edema. That is consistent with our study: periorbital edema represents 12% of skin adverse effects.
We also documented 3 cases of eczematous dermatitis successfully treated with topical steroids, 2 cutaneous

mycosis which of one extend to the body and face in a patient with artificial depigmentation prior to imatinib who also developed large stretch marks, and 2 patients with alopecia. The others skin reactions due to imatinib in our cohort were 1 onychodystrophy which disappeared while the nails were growing, 1 folliculitis, 1 stomatitis, 1 fixed pigmented eruption and 1 lichenoid reaction, which was treated without IM suspension, as described in following studies [17-19].

Maculo-papular eruption has been described as one of the most common adverse skin effects [3, 4, 14] but none of our patients presented such eruption.

Adverse skin effects are dose dependent [20] but seems not to be correlated to patient's age and sex. However, Scheinfeld [21] found a correlation between the young age and development of hyperpigmentation, and Ugurel *et al.* [20] found that women develop more hyperpigmentation and periorbital edema. In our study, adverse skin effects were also correlated to overall hematologic side effects. However, there is no correlation with each individual hematologic side effects, possibly because of low sample size. To our knowledge, such correlation has not been founded before. More study is needed to show that correlation.

At the end of our study, Imatinib mesylate therapy had been temporally suspended in the 3 cases of Stevens-Johnson and two other patients stopped voluntarily. However, the withdrawal of this drug, may compromise cancer treatment. Park and al successfully treated a patient with imatinib-induced DRESS syndrome with reslizumab, an interleukin-5 monoclonal antibody, while continuing IM treatment [22].

None of the other affections needed drug interruption, and they disappear with treatment excepted, for the pigmentary disorders.

Fig 1: Twenty-seven years old patient presenting generalized hypopigmentation 2 months after IM therapy. A) before therapy B) after therapy

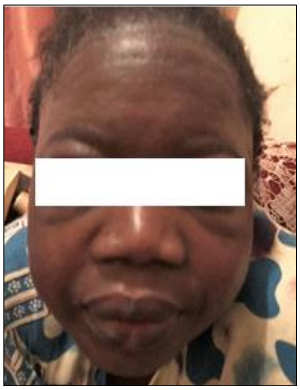

Fig 2: Periorbital edema

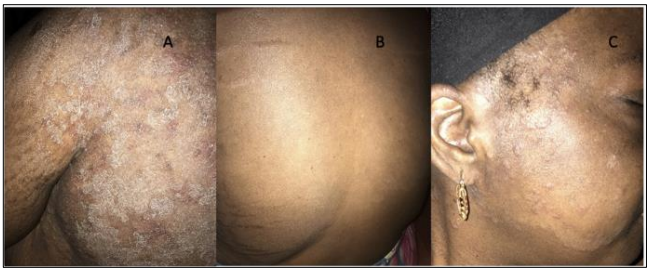

Fig 3: Cutaneous mycosis extended to the whole body and face A) Scapular localization 4 months after imatinib therapy B) Back after 1 month of antifungal treatment C) Face before treatment

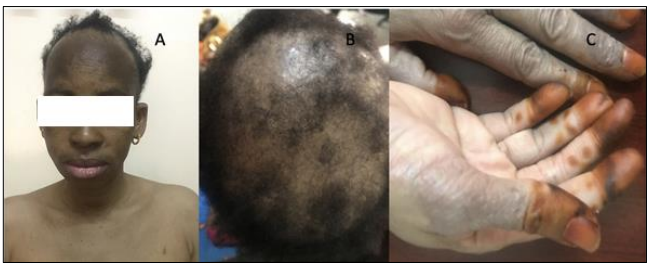

Fig 4: Fifty-three years old patient presenting both generalized hypopigmentation and frontal hyperpigmentation (A) associated with alopecia (B) and eczematous dermatitis (C)

Conclusion

Imatinib mesylate is a well-tolerated therapy and its cutaneous adverse effects are safely treated. An interesting finding of our study has been a rare case of a paradoxical association of hypopigmentation and hyperpigmentation in the same patient. The suspension of IM for dermatological complications is necessary only in rare cases, as shown by the low number of patients (n=3). Therefore, skin adverse effects should be diagnosed and treated early to improve therapy adherence specially for patients with few therapeutic alternatives.

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