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Adverse effects of Imatinib Mesylat: 5-year follow-up of 55 patients with chronic myeloid leukemia in Dakar (Sénégal)

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Keywords: chronic myeloid leukemia, Imatinib Mesylat, adverse effects, Dakar

ABSTRACT

Introduction: *Imatinibmesylate has significantly improved the survival of patients with chronic myeloid leukemia, with less toxicity than previous chemotherapy.*

Methods: *We describe the profile of hematological side effects or not Imatinib mesylate; through a retrospective study of 1 June 2006 to 31 June 2011, led to the unity of Hematology Le Dantec in Dakar (Senegal) in patients with chronic myeloid leukemia, imatinibmesylate treated. Chemotoxicity was classified according to WHO grades.*

Results: *A total of 55 patients followed; 24 (43.6%) had non-hematological side effects of grade 1-2, dominated by diffuse depigmentation (15 cases), followed by musculoskeletal symptoms (10 cases), digestive (6 cases), infection (4 cases) and secondary amenorrhea (1 case). Cytopenias observed in 34 patients, were more grade 1-2 (58.2%).*

Conclusion: *The side effects are common, rarely severe as reported in the literature. Our study is unique in the high frequency of diffuse depigmentation unlike western series.*

INTRODUCTION

Imatinibmesylate (IM) is the only tyrosine kinase inhibitor (TKI) first generation available in Senegal since 2006 with GIPAP (Glivec International Patient Assistance Program). He revolutionized the natural history of chronic myeloid leukemia (CML) with less toxicity than previous chemotherapy [1]. Our aim was to describe the profile, the prevalence and prognostic impact of the adverse effects of MI in our patients with CML.

METHODOLOGY

We conducted a retrospective study of 5 years (June 1, 2006- June 31, 2011), the Unit of Clinical Hematology University Hospital Le Dantec in Dakar (Senegal) in 55 patients with CML. The diagnosis was retained before the presence of Philadelphia chromosome and / or Bcr / Abl. In the chronic phase, the IM was given at a dose of 400 mg / day in adults and 300mg / day for adolescents. Accelerated or acute phase of MI was administered at a dose of 600mg / day in adults

and 400 mg / day in adolescents. The WHO classification of chemical toxicity was used [2]. We conducted prevalence analyses and multivariate to search for prognostic factors.

RESULTS

Our sample consisted of 29 women and 26 men who had the clinical and biological characteristics reported in Table I.

Table I: Characteristics of our study population

Signs	Number (%)	Average	Extremes
Age (year)	35,9		[9-74 ans]
Splenomegaly II-III	12 (21,8)		
Splenomegaly IV-V	35 (78,2)		
Diagnostic phase			
chronic	39 (70,9)		
accelerated	13 (23,6)		
acute	3 (5,5)		
Blood count			
White bloodcells (/mm ^{3})		312533,82	[4000 - 5063700]
Haemoglobin (g/dl)		9,1	[5,3 - 13,8]
Neutophils (%)		48,4	[26- 92,8]
Platelets(/mm ^{3})		467778,18	[38400 -1 485000]
Cytogenetic			
Isolated philadelphiachromosom	34 (61,8)		
Superadded genetic abnormality	21 (21,2)		

Table II: Hematologic and non-hematologic toxic effects of Imatinib

Non haematologictoxicity	**Grade 1-2**	**Grade3-4**
Dermatologic	**N (%)**	**N (%)**
Diffuse depigmentation	15 (27,3)	
Dysidrosis	1 (1,8)	
Musculoskeleton		
Cramps	6 (10,9)	
Edema	4 (7,3)	
Digestive		
Vomiting	4 (7,2)	
Diarrhea	2 (3,6)	
Infectious		
Cellulitis	3 (7,2)	
Pericarditis	1 (1,8)	
Haematologic toxicity		
Leukopenia	2 (58,2)	5 (9,1)
Neutropenia	24 (43,6)	17 (30,9)
Anemia	31 (56,4)	11 (20)
Thrombopenia	10 (18,2)	9 (16,4)

Non-hematologic side effects noted in 24 patients, all were grade 1-2 (Table II). They were dominated by diffuse depigmentation, isolated without pruritus. About dyshidrosis, it was regressive with local topical corticosteroid application. Musculoskeletal signs were dominated by cramps, which had declined in systematic administration of calcium and magnesium. The calcium and phosphate levels werenot made. Edema was mainly periorbital (4 cases) and widespread in 1 patient polyvalvular withcongestive heart failure.

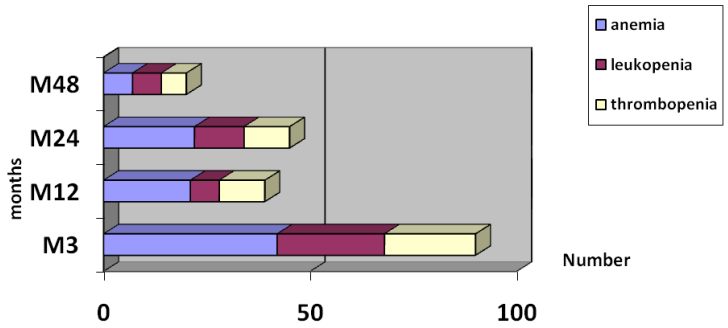
The digestive symptoms dominated by vomiting, disappeared after fragmentation of twice-daily doses (3 cases) or taking Domperidone (2 cases). Non febrile diarrhea was functional without isolated germs.

Infections complications were a felon (2 cases), post streptococcal cellulitis of the leg (1

case), and purulent pericarditis associated with pneumococcal bacterial endocarditis (1 case); treated with appropriate antibiotic therapy.

Haematologic toxicity was noted in 34 patients among whom more than half had Grade 1-2cytopenia (Table II) Cytopenia grade 3-4 rarer occurred in patients treated at a dose of 600mg / day. The dose of Glivec was temporarily suspended and / or reduced in 11 cases of thrombocytopenia and 3 neutropenia. Stopping Glivec was indicated in 3 cases of acute leukemia with severe cytopenia. The overall haematological toxicity was less frequent beyond 24 months (Figure 1).

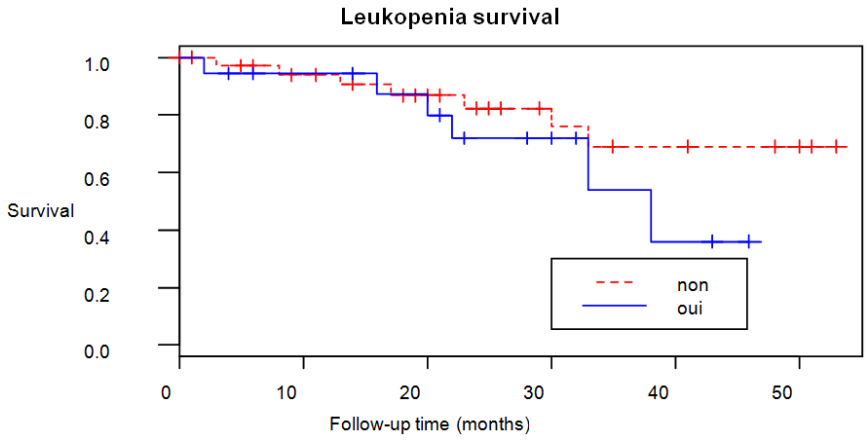
Figure 1: Effective cytopenia in time



Evolutionarily were noted a complete hematologic response in 97.9% of cases, major cytogenetic in 60% of cases, minor in 15% and minimum in 25% of cases. We noted 12 deaths (22.2%), in an array of acute myeloid leukemia (10 cases), 2 cases of sudden death.

In multivariate analysis, leukopenia was associated with reduced survival (Figure 2).

Figure 2:



DISCUSSION

The adverse effects of MI are divided into non-hematological and hematological toxicities, variously reported by the authors [1, 3]. They are mild as observed in our patients [1], more frequent during the first two years of treatment [3].

Non-hematological toxicities were dominated by diffuse depigmentation in our study. However localized forms are described. [4] This depigmentation was linked to the effects of IM on the receiver Kit and sterm cell factor (SCF), which play a role in the synthesis, differentiation and survival of melanocytes [4]. Sun exposure is a risk factor that may partially explain its high prevalence in our study. Diffuse depigmentation presents a racial distribution because most reported in black patients. [4] However, Raanani et al [5] published a finding in a Caucasian; similarly, the lack of specificity to the skin histology, question the racial theory [4, 5]. Other lesions like vitiligo appearance, lichenoid eruptions, pityriasisrosea, hyperpigmentation and epidermolysis are described in the literature [6].

Other toxic effects are edema, cramps, digestive disorders are variously reported and managed symptomatically [1, 7]. Infectious complications would be favored by hypogammaglobulin and alteration of lymphocyte functions T and NK [7].

As for haematological tolerance; it was rarely severe grade 1-2 in our study, according to the literature [3, 8]. Hematologic toxicity is increased by high doses. [8] Hematologic side effects concern all blood lineages, particularly the buffy neutropenia, which is correlated to the decrease in survival in our patients. Other cytopenias are more frequently anemia as thrombocytopenia. The latter would be a poor prognostic factor. [9] The management of these toxic cytopenia is codified according to consensus [1, 3].

CONCLUSION

We reported multiple toxic effects of Imatinib Mesylate. They are rarely severe as described in the literature. This particular study is the high incidence of depigmentation diffuse unlike western series.

CONFLICT OF INTEREST

None.

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