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Therapeutic drug monitoring of imatinib in patients with chronic myeloid leukaemia: Experience from Oran HUE

Hamza BENBACHIR [1,*], Hichem NAAS [2], Hichem BOUGUEDRA [1], Souad GENDOUZ [3], Badra ENTA SOLTAN [4], Hassan CHADOU [1], Amina AMIAR [1], Nabil YAFOUR [4] and Houari TOUMI [1]

[1] *Pharmacovigilance department, University Hospital Establishment of Oran, Algeria.*
[2] *Mohamed Lamine Debaghine University Hospital Center, Algiers, Algeria.*
[3] *Tlemcen Faculty of Medicine, Abu Bakr Belkaid University, Tlemcen, Algeria.*
[4] *Hematology department, University Hospital Establishment of Oran, Algeria.*

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Abstract

Imatinib, a first-line treatment for chronic myelogenous leukemia, presents significant interindividual pharmacokinetic variability. The correlation between the plasma exposure of Imatinib and its pharmacological effects makes this drug a good candidate for pharmacological therapeutic monitoring in addition to the usual monitoring tests. We introduced monitoring of Imatinib in 27 patients suffering from chronic myelogenous leukemia. According to the dosage results, dosage adaptation recommendations were proposed to clinicians in patients outside the targeted therapeutic range. The goal was to achieve an optimal response to Imatinib, prevent its adverse effects and improve adherence to treatment.

Keywords: Imatinib; Therapeutic drug monitoring; Chronic myelogenous leukemia; Dosage adaptation; Major molecular response

1. Introduction

Imatinib, the leading tyrosine kinase inhibitor (TKI) is the reference and first-line treatment for chronic myelogenous leukemia (CML) in Algeria [1].

At standard doses of Imatinib, around 30% of patients are underdosed, which implies a risk of reduced efficacy, or even therapeutic failure, while around 15% of patients are overdosed, potentially being exposed to preventable toxicities [2].

The demonstration of a link between the residual plasma concentration of Imatinib (C_{res})and the achievement of an optimal pharmacological response in patients with CML, served as proof of the interest of therapeutic drug monitoring (TDM) of this medicine [3, 4.5].

The objective of our work was to introduce TDM and dosage adaptation of Imatinib in patients with CML, followed at the Oran University Hospital (HUEO), to optimize therapeutic results and prevent avoidable adverse effects.

2. Material and Methods

Our study took place over a period of 7 months, from March 1, 2021, to October 31, 2021, in Pharmacovigilance department of the HUEO in collaboration with Hematology department.

* Corresponding author: Hamza BENBACHIR.

We included patients aged over 18 years, on Imatinib for at least 1 month, suffering from CML in chronic phase and whose Philadelphia chromosome or its molecular equivalent was detected at diagnosis.

Data collection was carried out using a questionnaire at the time of consultations, by interaction with the patients, the attending physician and by study of medical records. Statistical analysis of data has been done using Excel® and SPSS® programs.

A method for measuring plasma Imatinib by high performance liquid chromatography coupled to a diode array detector (Table 1), has been developed and analytically validated to meet the requirements of the TDM in terms of reproducibility and fidelity. An Imatinib Cres assay was performed for each patient, alongside routine assessments.

Table 1 Characteristics of the Imatinib dosing method

HPLC chain	**ULTIMATE 3000 thermo scientific®**
Column type	C18
Column dimensions	250mm*4.6mm*5µm
Detector type	Diode array detector
Wavelength (λ)	265nm
Retention time	4 to 5 mins

From the various studies carried out on the concentration-effect relationship of Imatinib [3-6], we chose the value 1000 ng/ml as the target residual plasma concentration, making it possible to achieve the therapeutic objective in terms of efficacy. The value 1500 ng/ml was adopted as a tolerance threshold value, beyond which, the probability of toxicity of Imatinib increases, without improving the efficacy, for the lower limit, we tolerated Cres up to 850 ng/ml before adjusting the dose.

The Imatinibemia results obtained in patients with CML were interpreted according to the therapeutic interval [850-1500] ng/ml, the clinical context of the patient, the previous results of evaluation of the molecular response and the profile of tolerance to Imatinib. This allowed us to establish the link between the C_{res} and the various adverse events, represented by treatment failure, disease progression, suboptimal response, treatment intolerance, drug interactions and non-compliance.

Taking into consideration the linear pharmacokinetics of Imatinib as well as the different pharmaceutical forms available in Algeria, and based on studies aimed at demonstrating the interest of the TDM of Imatinib in routine [7,8], an algorithm for dosage adaptation of Imatinib according to C_{res}, was developed to facilitate the individualization of doses (Figure 01), the objective was to target a C_{res} of 1,000 ng/ml.

Our approach was initially to adopt a therapeutic interval which takes into consideration the efficacy threshold values proposed by the majority of studies, including a recent Algerian study [5] in addition to a tolerance threshold value which allows reducing the probability of appearance of dose-dependent adverse effects, this allowed us to work on optimizing the response on both levels, effectiveness and toxicity. Secondly, based on the C_{res} found and after interpretation of the results, we proposed dosage adaptation recommendations to correct the Imatinibemia of patients whose values are outside the therapeutic range. Finally, we opted for an evaluation of the impact of the proposed interventions on the response to long-term treatment so that the proposed algorithm can be improved.

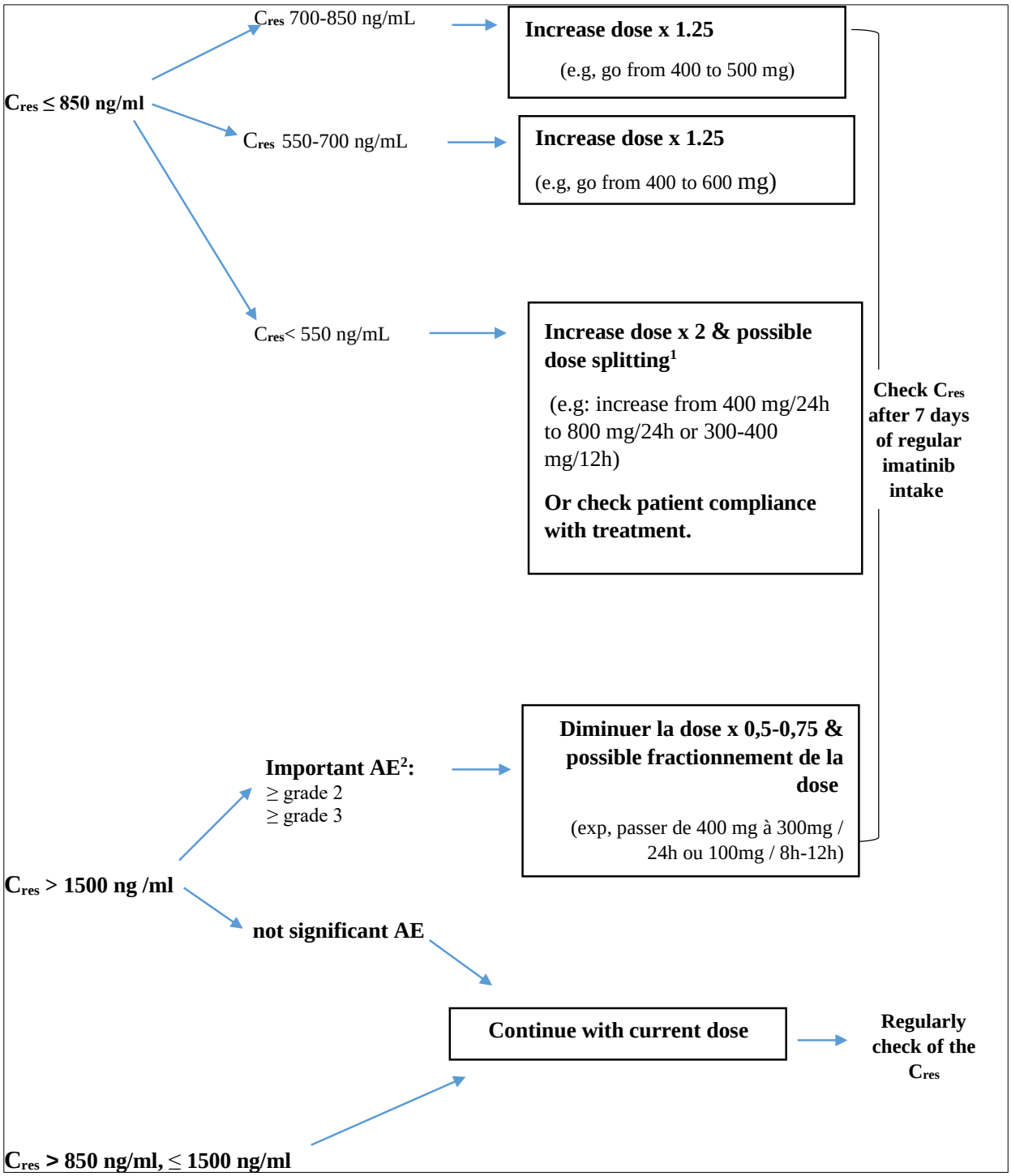

Figure 1 The imatinib dose adjustment algorithm based on trough concentration**.**

[1] Splitting the total daily dose into two doses allows you to achieve a higher C_{min} and a lower C_{max} than with a single dose per day.

[2] Adverse event

3. Results and discussion

Our study was carried out on 27 patients, The sex-ratio (M/F) of our population is 0.8, The average age is 53 years, the median age is 55 years (Table 2), a peak frequency is observed in the age group of 50 to 64 years, these data are slightly higher than those described in the study by Reggabi (median age: 47 years and peak in the age group: 40 to 49 years) and Djouadi (median age: 43.5 years and peak age range: 36 to 45 years) [5.9].

The distribution of patients according to the dosage of Imatinib, at inclusion, at the time of the first dosage carried out in the patient, shows that 89% of patients were on a dosage of 400 mg/day. 3.7% and 7.4% were respectively on a dosage of 300 mg/day and 200 mg/day. Approximately 41% of patients had an associated condition and were receiving other medications in addition to Imatinib.

Table 2 Data relating to patient age

Gender	Effective	Extremes Values	Average	Median	Gap-kind
Man	12	18 to 74	52.92	56.5	18.2
Women	15	30 to 73	53.67	55	11.65
Total	27	18 to 74	53.33	55	14.61

The evaluation of compliance with treatment according to the investigator's estimation shows that 18% of patients are judged to be non-compliant to moderately compliant. Even if the judgment criteria according to the investigator may contain amount of subjectivity, a significant link was highlighted between compliance and the C_{res} of Imatinib (Khi_2 test, p = 0.001). From there, particular importance was given to the therapeutic education of patients presenting problems with adherence to treatment.

Evaluation of the molecular response shows that 78% and87% of patients achieved, respectively, a major molecular response (MMR: bcr-abl ratio <0.1%)at 12 months and18months of treatment(Table 3),the accumulation of patients who obtained an MMR between 12 and 18 months is notable. Achieving an MMR at 12 months is considered the optimal response to treatment according to the ELN "EuropeanLeukemiaNet", the national CML working group tolerates an MMR up to18 months. The study carried out by Reggabi reported MMR rates of 56.4% at 12 months and 84.8% at 18 months[5].Abdennebi et al reported MMR rates of 65% at 12 months and 80% at 24 months[1]. An MMR rate of 80% was recorded during the IRIS study [10].

At inclusion, considering the last molecular evaluation of all patients with a treatment duration of 12 months or those whose molecular response was completed before 12 months (only 1 patient), made it possible to identify a MMR in 72% of patients. This difference with the MMR rate at 12 months and 18 months is justified by the fact that some patients acquired previously an MMR lost it later, while some reached late MMR. In these patients, the variability in the response to treatment over time is often justified by periods of significant interruption due to the shortage of Imatinib. Table 2 shows the characteristics of patients not included in the count during molecular response assessment.

Table 3 Features patients not included in the count when evaluating the molecular response**.**

*1st sample for imatinib dosage	At 12 months of treatment	At 18 months of treatment	On inclusion*
Processing time not completed	5	7	3
Assessment not done	4	4	6
Total	9	11	9

The inventory of adverse effects of Imatinib shows that 6 types of effects are found in more than 30% of patients (Figure 2). Myalgia and muscle cramps in 1st place with a rate of 55%, comparable to that observed in the study carried out by Reggabi [5]: 56% and the IRIS study [10]: (49%) but much higher than that reported by Djouadi and al [9]: 24%. They are followed by bone pain 48% (versus 25% according to Reggabi and 18% according to Abdennebi and al [1]. Hematological toxicities represented by anemia, thrombocytopenia and neutropenia occupy an important place with respective rates of 44%, 37% and 29%. Oedema and fluid retention are reported in 22% of our effectif, occupying 1st place among adverse effects described in the IRIS study (60%) and 3rd place among adverse effects reported by Reggabi with a rate of 32%.

Most adverse effects reported in our study are grades 1 to 2. Grades 3 and 4 adverse effects mainly concern haematological toxicities and are the most important reason for temporarily stopping treatment (Table 4).

Table 4 Adverse effects and hematological toxicities of imatinib distributed by grade in the study population.

Adverse effect / Toxicity	**Number of patients (%)**	**Grade**			
		1*	2*	3*	4*
Anemia	12 (44.44%)	5 (41.66%)	2(16.66%)	3(25%)	2(16.66%)
Neutropenia	8 (29.62%)	1(12.5%)	1(12.5%)	4(50%)	2(25%)
Thrombocytopenia	10 (37.03%)	2(20%)	2(20%)	5(50%)	1(10%)

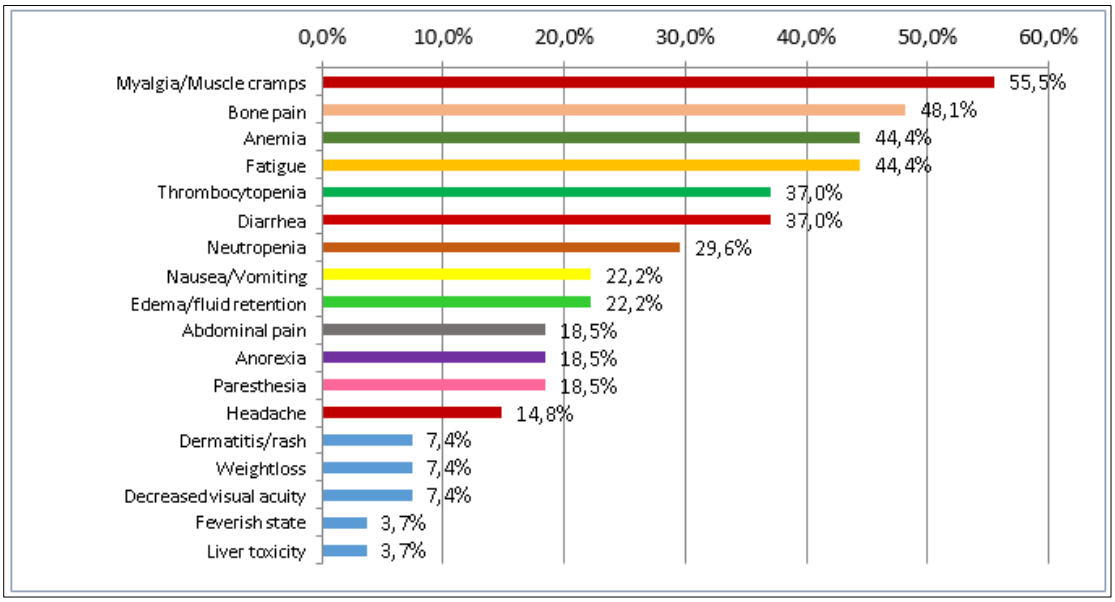

Figure 2 Adverse reactions and toxicities of imatinib reported in the study population

To study the relationship between the C_{res} of Imatinib and the achievement or not of an optimal response (MMR) at inclusion, we selected patients whose last molecular response assessment corresponded to the date of inclusion. 16 patients were selected and divided into two groups, responders (MMR+) and non-responders (MMR-). Analysis of the results shows an average C_{res} of**1194.45**±396.91ng/ml with extreme values ranging from**295.2 to 2076.34** ng/ml. These results are comparable to those reported by Reggabi [5]: 1226.9 ± 565.6 ng/ml after 12 months of treatment, but higher than those of Picard [4]: 1058 ± 557 ng/ml after at least 12 months of treatment. The comparison between the means of Imatinib C_{res} in responders and non-responders revealed a significant difference between the two groups (Wilcoxon test for equality of means, $p < 0.05$), which confirms the link between obtaining an MMR and the Cres of Imatinib as reported by several studies [3-6] (Figure 3).

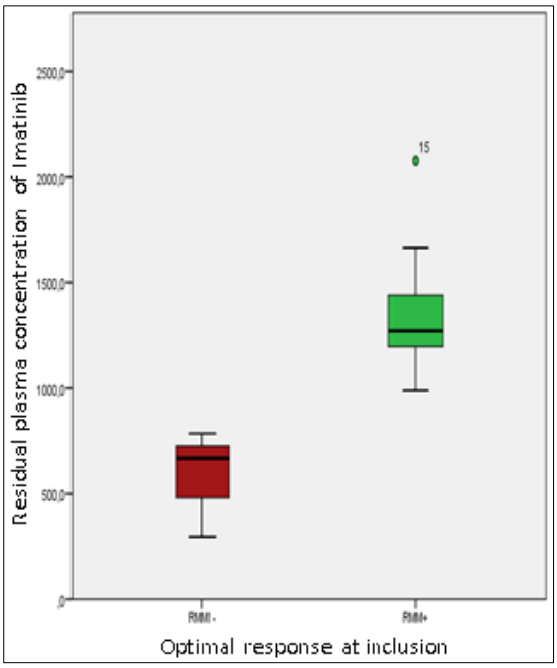

Figure 3 Comparison of mean plasma trough concentrations of Imatinib in responders and non-responders at baseline

The distribution of Imatinib Cres, carried out in 27 patients in our study, shows that 59% (16/27) of patients are in the therapeutic range (850-1500 ng/ml), while 26% (7 /27) and 15% (4/27) of patients have, respectively, subtherapeutic(<850ng/ml) and supratherapeutic (>1500 ng/ml) concentrations (Figure 4).

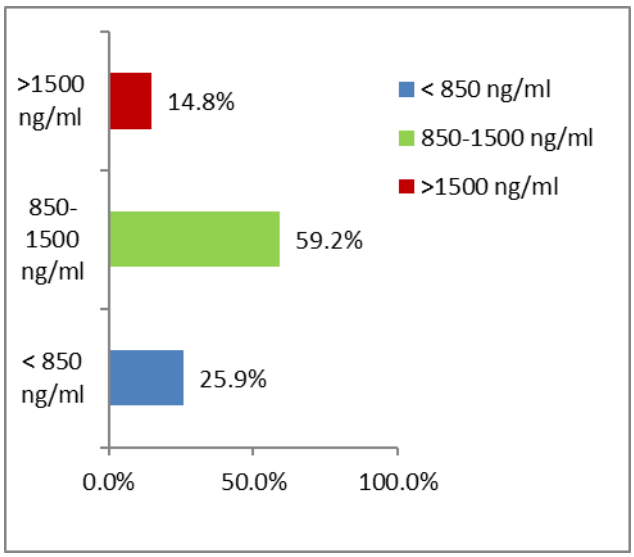

Figure 4 Distribution of residual concentrations of imatinib according to the therapeutic range

At patients with low C_{res} (<850 ng/ml): 42.8% (3/7) did not have an MMR at inclusion, therefore considered non-responders (RMM-), in practice, more than 30% of patients discontinue Imatinib due to unsatisfactory efficacy or intolerance [2.5]. This could be partly overcome by appropriate dosage modifications. For the remaining 57% (4/7) of patients, although previous evaluations showed an optimal response was achieved, the absence of a recent evaluation of the bcr-abl transcript at inclusion prevented us from defining the treatment response status, after analysis, it turned out that these 4 patients were only moderately compliant**, i.e.,** showed fluctuations in taking Imatinib (Figure 5).

Normo-therapeutic patients (850 ng/ml <Cres< 1500 ng/m): 68.7% (11/16) presented an MMR (optimal response), which demonstrates the interest in situating patients around a value target of 1000 ng/ml to achieve the therapeutic

objective in terms of efficacy. 31.2% (5/16) of patients located in the targeted range (850-1500 ng/m), were not evaluated at inclusion following the absence of a recent evaluation of the bcr-abl transcript, among them, 4/5 had a duration of treatment with Imatinib ranging from 3 to 5 months, therefore recently placed on Imatinib (Figure 5). An early C_{res} situation near of efficacy threshold value (≥ 1000 ng/ml), promotes the achievement of a major molecular response at 12 months (optimal response). According to Reggabi [5], the study of the predictive potential of early determination at 1 month of the C_{res} of Imatinib, on the optimal response at 12 months of treatment, with exclusion of non-compliant patients, showed a significant difference between the average concentrations of the responder groups and non-responders. This proves the existence of a link between the residual plasma concentration of Imatinib obtained at 1 month and the molecular response at 12 months.

Patients with supra-therapeutic C_{res} (C_{res}>1500 ng/ml): among 4 patients, 2/4 (50%) are responders (MMR+), 1/4 (25%) presents a non-optimal response, in this last patient despite an increase well above the targeted 1000 ng/ml, the bcr-abl ratio increased from 1.6%(6 months of treatment) to 21%(12 months of treatment), which demonstrates therapeutic failure **(**Figure5).

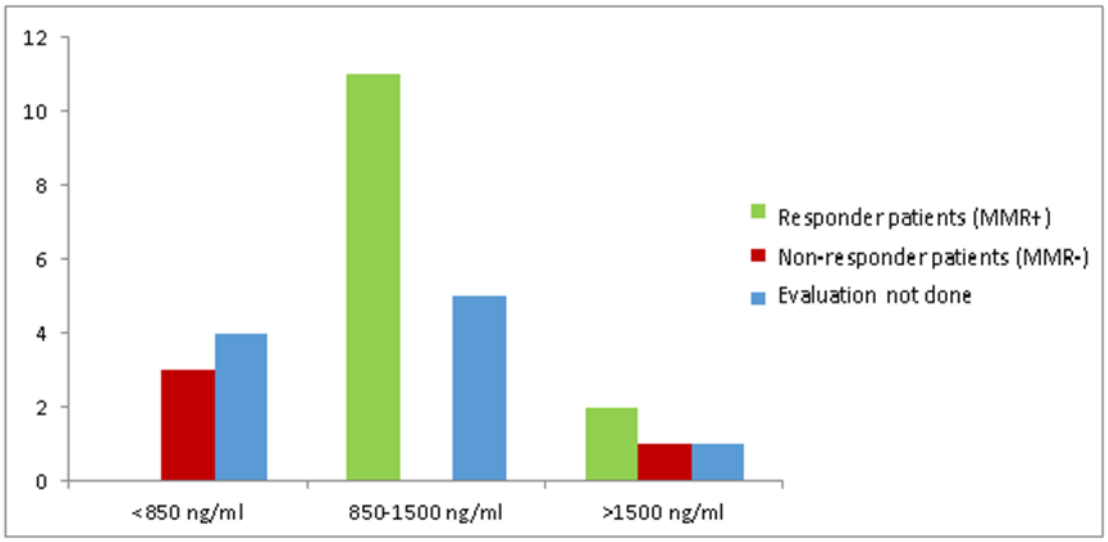

Figure 5 Distribution of imatinb residual concentrations according to whether or not an optimal response was obtained (RMM: bcr-abl <0.1%) at inclusion.

Based on algorithm dosage adjustment (Figure 1), recommendations for dosage optimization have been proposed to correct the Imatinibemia of patients whose values are outside the therapeutic range. In underdosed patients, the strategy consists of firstly eliminating a cause of non-compliance, then secondly, insufficient exposure to Imatinib, both of which are considered factors of pharmacokinetic variation, exposing the risk of progression and or therapeutic failure. The procedure to follow would be to optimize the therapeutic education of patients in the event of poor compliance, or to individualize the dosage, adapting it to the context, in the event of insufficient exposure. However, a reduction in dosage has been proposed if the *C_{res}> 1,500 ng/ml* accompanied by moderate (grade 2) or severe (grade 3) adverse effects.

Among the 11 patients outside the targeted therapeutic range, a dosage adjustment was proposed in 4 patients: an increase in the dose in 2 patients and a reduction in the dose in 2 others. Two patients were switched to a 2nd generation TKI, following intolerance for the first and therapeutic failure for the first. Other problem of Compliance was reported in 5 patients for whom we carried out therapeutic education sessions to improve adherence to treatment. Table V shows the characteristics of patients outside the therapeutic range as well as the recommendations issued for each case.

Table 5 Different characteristics of patients located outside the therapeutic range

Patient	Duration of treatment	Un favorable events	Dose /d	Created	Recos TDM	Effectiveness at inclusion	AE at inclusion
F, 58 years old	> 48	Intolerance, progression	300 mg	295.00	Therapeutic education, switch	loss of MMR	muscle cramps G2/bone pain G2 to G3
F, 53 years old, 45 kg	> 48	observance	200 mg	489.27	Therapeutic education	Assessment not done	anemia G2/neutropenia G3
M, 63 years old, 70 kg	16	Suboptimal response	400 mg	667.26	↑at 600 mg/d	no RMM	muscle cramps G1
M, 44 years old, 92 kg	> 48	Non-compliance	400 mg	721.83	Therapeutic education	Assessment not done	/
M, 53 years old, 79 kg	> 48	Progress	400 mg	784.04	↑at 500 mg/d	loss of MMR	/
M, 74 years old, 70kg	> 48	Non-compliance	400 mg/d	812.45	Therapeutic education	Assessment not done	abdominal pain G1/arthralgia G1
F, 49 years old, 65 kg	> 48	Non-compliance	400 mg*d	817.8	Therapeutic education	Assessment not done	muscle cramps G1 to G2/ bone pain G1 to G2
F, 39 years old, 80 kg	32	Intolerance	400 mg	1664.0	↓ to 300 mg/d	RMM	osteo-muscular pain G2/ abdominal pain G2
F, 66 years old, 58 kg	> 48	/	400 mg	1565.32	/	Assessment not done	diarrhea G1/ paraesthesia G1
F 30 years old, 75 kg	16	Failure, Intolerance	400 mg	1717.95	Stop, switch	no RMM	NV G2/ abdominal pain G2/ muscle cramps G2
M, 47 years old, 65 kg	5	Intolerance	400 mg	2076.34	↓ to 300 mg/d	RMM	thrombocytopenia G3

4. Conclusion

The Imatinib TDM constitutes an excellent complement to the usual biological monitoring tests for patients with CML and provides a tool to help clinicians optimize treatment in terms of effectiveness and toxicity.

The introduction of Imatinib TDM into clinical practice will help avoid unnecessary switches to second-generation tyrosine kinase inhibitors, which increase the cost of treatment and disrupt the pharmaco-economic balance.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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