Short Communication

The clinical relevance of imatinib plasma trough concentrations in chronic myeloid leukemia. A Belgian study

Florence Van Obbergh [a], Laurent Knoops [b], Timothy Devos [c], Yves Beguin [d], Carlos Graux [e], Fleur Benghiat [f], Khalil Kargar-Samani [g], Deborah Bauwens [h], André Efira [i], Christian Dubois [j], Cécile Springael [k], Luc Montfort [l], Thierry Connerotte [m], Arnaud Capron [n], André Delannoy [a,*,1], Pierre Wallemacq [n]

[a] Hematology Department of CH Jolimont, La Louvière, Belgium
[b] Hematology Department of Cliniques, Universitaires St Luc, Brussels, Belgium
[c] Hematology Department of UZ Leuven, Belgium
[d] Hematology Department of CHU Liège, Belgium
[e] Hematology Department of CHU Dinant Godinne, Belgium
[f] Hematology Department of CHU Erasme, Brussels, Belgium
[g] Hematology Department of CHWAPI, Tournai, Belgium
[h] Hematology Department of Clinique St Jean, Brussels, Belgium
[i] Hematology Department of CHU Brugmann, Brussels, Belgium
[j] Hematology Department of Cliniques de l'Europe, Brussels, Belgium
[k] Hematology Department of CHU Tivoli, La Louvière, Belgium
[l] Hematology Department of St Luc, Bouge, Belgium
[m] Hematology Department of St Pierre, Ottignies, Belgium
[n] Clinical Chemistry Department, Cliniques Universitaires St Luc, Brussels, Belgium

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ABSTRACT

This retrospective multicenter study in patients with chronic myeloid leukemia in chronic phase was undertaken to confirm the clinical relevance of imatinib plasma concentrations monitoring in daily practice. Forty-one patients, with 47 imatinib plasma measurements, were analyzed during treatment with imatinib given at a fixed 400 mg daily dose. A significant inverse relationship of imatinib concentration with the patients' weight was observed (Pearson's test: $p = 0.02$, $R^2 = 0.1$). More interestingly, patients with poor response (switched to another tyrosine kinase inhibitor because of imatinib failure, or because of disease progression after an initial response) displayed a significantly lower mean imatinib concentration as compared to patients maintained on imatinib (822 ng/mL vs 1099 ng/mL; Student's t-test, $p = 0.04$). Failure or disease progression occurred more often in patients in the lowest quartile of imatinib concentrations compared to patients in the highest quartile ($p = 0.02$, logrank test). No correlation could be established with other biological or clinical parameter, including complete cytogenic response and major molecular response. In conclusion: in patients treated with imatinib at a fixed daily dose of 400 mg, imatinib plasma concentrations decreased with increasing body weight and were lower in patients switched to another tyrosine kinase inhibitor due to imatinib failure. Systematic determination of imatinib plasma trough levels should be encouraged in such patients.

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1. Introduction

The course of chronic myeloid leukemia (CML) has dramatically improved since imatinib mesylate (IM), the first member of a family of tyrosine kinase inhibitors (TKI) with BCR-ABL1 blocking activity, was made available for clinical use [1]. In contrast with most *anti*-cancer drugs, IM and next generation TKIs are administered at fixed dose (most often 400 mg of IM daily during the chronic phase of the disease) irrespective of the patient's physical characteristics, including weight, body surface and body mass index (BMI). Yet, a wide variation of plasma trough IM concentration was repeatedly demonstrated in such patients according to weight, interaction with concomitant drugs, malabsorption, renal and hepatic functions, genetic factors and, last but not least, as a function of patient compliance with treatment [2]. IM concentration correlates with cytogenetic and molecular response

to treatment, which, in turn, correlates with clinical outcome [3]. Picard et al. determined that the ideal trough IM plasma concentration should be at least 1000 ng/mL [4].

Since 2009, IM plasma concentration assessment was made available to Belgian hematologists on a voluntary basis. Meanwhile, second generation TKIs became available in Belgium for patients with intolerance or after failure of IM. Change of treatment to the new TKIs after failure of IM provided us with a new operational definition of IM failure. In this work, we analyzed the clinical relevance of IM therapeutic drug monitoring in patients with CML in the chronic phase including an analysis of the relationship between IM trough concentrations and treatment failure, defined by a change of TKI for resistant or relapsing disease.
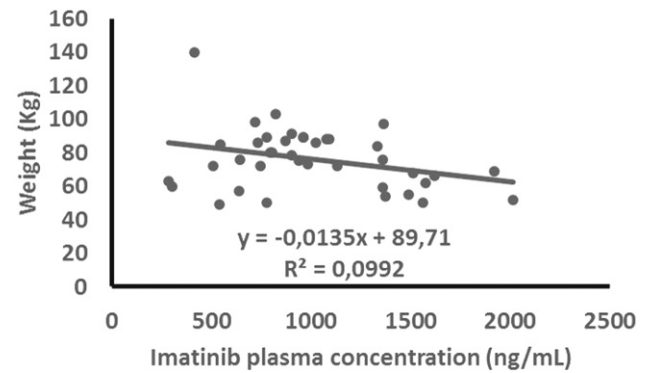
2. Patients and methods

This is a retrospective multicenter study performed in Belgian hematology departments who volunteered to communicate clinical data on patients with CML treated with IM, and with at least one IM plasma (EDTA) concentration assessment. IM concentrations presented here were determined by a liquid chromatographic tandem mass-spectrometric method (LC-MSMS) in the laboratories of UCL St Luc University Hospital, Brussels, as described elsewhere [5], and of the University Hospital, Leuven (UZ Leuven). Only patients with chronic myeloid leukemia in chronic phase treated with IM 400 mg daily were analyzed after obtaining the ethics committee approval in hospitals requesting such an approval for retrospective studies. This study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. Cytogenetic response was complete if no Ph1 chromosome was observed after analyzing at least 20 metaphases, while a major molecular response was defined by a BCR-ABL1 expression ≤0.1%, according to the European Leukemia Net recommendations [6].

Continuous data were correlated with the use of Pearson's test while categorical data were compared by Student's *t*-test after checking that data distribution was normal. Means are reported ± 2 Standard errors when appropriate. Failure or progression probability curves over time (defined by a change of TKI unrelated to intolerance to IM) were calculated according to Kaplan and Meier's estimate of survival method and were compared by the logrank test [7,8].

Fig. 1. Relationship between weight and plasma IM concentration. The inverse correlation between weight and IM plasma concentrations is significant ($p = 0.02$, Pearson's test).
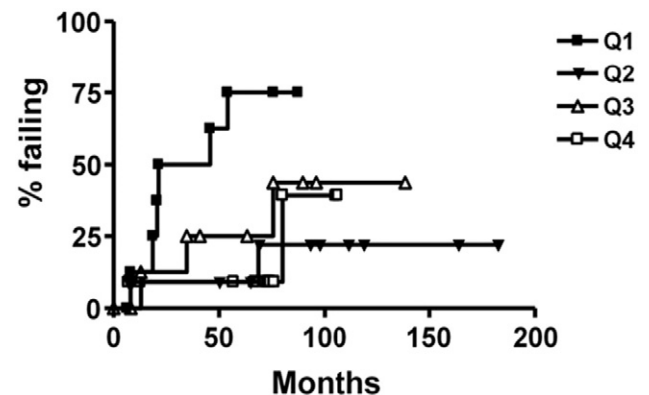
3. Results

Forty-one patients involving 47 IM plasma concentrations were analyzed. The main clinical data at IM concentration measurement, response to therapy, and outcome are summarized in Table 1. During follow-up (median duration: 6.1 years) CML acceleration was observed in 2 cases. Thirteen patients had to change to another TKI because of molecular resistance or progression on IM. In addition, 4 patients were switched to nilotinib or dasatinib because of intolerance to IM.

Correlations studies showed a significant inverse relationship of IM concentration with weight ($p = 0.02$), as shown in Fig. 1, and with height ($p = 0.02$). Body surface, mass index and age did not correlate with IM concentrations.

Categorical data analysis showed a lower mean IM concentration (822 ng/mL ± 200) in patients who later changed to another TKI because of poor molecular response (8 patients) or molecular disease progression (5 patients) compared to patients who were maintained on IM (24 patients) or who changed to another TKI because of intolerance to IM (4 patients) (mean IM concentration 1099 ± 156 ng/mL, $p = 0.04$, Student's *t*-test). Cytogenetic and molecular response did not correlate with IM concentrations.

Finally, we tried to confirm the link between IM concentrations and CML progression by assessing the progression-free survival in the four quartiles of patients defined on the basis of IM concentrations, from the first quartile (Q1) with the lowest IM concentrations, to the fourth quartile (Q4) with the highest IM concentrations (Fig. 2). Progression probability over time in patients in the lower IM quartile (Q1) was statistically higher by the logrank test when compared to progression risk

Table 1
patient characteristics at IM plasma concentration measurement and outcome.

	n analyzed	Median	Range
Patients	41		
Age (years)	41	49	17–87
Sex: Male/female	23/18		
Weight (kg)	39	76	49–140
Height (cm)	31	169	148–200
Body surface area (m²)	31	1.89	1.43–2.79
BMI (Kg/m²)	31	26.2	18.4–35
IM concentration (ng/mL)	47	938	287–2013
Creatinine (mg/dL)	41	0.9	0.5–1.6
Time interval between diagnosis and first IM plasma concentration (years)	40	2.2	0.15–12.3
Sokal score at diagnosis: low-intermediate-high	18-12-3		
Hasford score at diagnosis: low-intermediate-high	17-10-1		
Eutos score at diagnosis: low-high	16-2		
Follow-up duration (years)	40	6.1	0.53–15.1
Cytogenetic response: complete-partial-failure	31-5-1		
Molecular response: major or complete-less than major	28-11		
Change of TKI: no-yes for failure-yes for toxicity	24-13-4		
Disease acceleration	2		
Transformation to acute leukemia	0		

Fig. 2. Progression or failure probability, according to plasma IM concentrations in the 41 patients. Failure or progression was defined as a change of TKI not related to intolerance to IM. Q1, Q2, Q3, and Q4 represent patients belonging to the first, second, third, and fourth quartile of IM concentrations, respectively, from the lowest to the highest IM concentrations. Time was calculated from diagnosis. Differences between Q1 and Q2 and between Q1 and Q4 are statistically significant (logrank test, $p = 0.02$).

in patients in Q2 ($p = 0.02$) and Q4 ($p = 0.02$). No significant progression difference could be established between patients in Q1 and Q3 ($p = 0.1$).

4. Discussion

This retrospective multicenter study confirms the inverse relationship between body weight/height and IM trough plasma concentrations, and does not support the use of fixed IM doses. In our study, no correlation with cytogenic failure could be demonstrated, probably because failures to achieve a complete cytogenic response were rare (6/37); molecular response failed to correlate with IM concentrations but molecular studies were not centralized in this retrospective study and thus proved difficult to compare. However, our data show that a low IM plasma trough concentration is associated with treatment failure defined as a change of TKI after failure of IM or after progression following a major response. In addition, a recent randomized study reported by Rousselot et al. strongly suggests that adapting IM dose in order to reach therapeutic plasma concentrations has a favorable impact on the treatment response, which strengthens our recommendation to perform IM therapeutic drug monitoring in CML patients [9]. This recommendation is particularly important in patients with risk factors for low IM concentrations (obesity, malabsorption, multiple medications…) but should be expanded to all patients as inappropriately low IM concentrations can be observed in patients with no risk factor and as poor compliance to treatment (approximately 30% of patients) can be suspected on the basis of unusually low concentrations or of hectic results [10].

References

[1] H. Kantarjian, S. O'Brien, E. Jabbour, G. Garcia-Manero, A. Quintas-Cardama, J. Shan, M.B. Rios, F. Ravandi, S. Faderl, T. Kadia, G. Borthakur, X. Huang, R. Champlin, M. Talpaz, J. Cortes, Improved survival in chronic myeloid leukemia since the introduction of imatinib therapy: a single-institution historical experience, Blood 119 (2012) 1981–1987.

[2] N. Takahashi, M. Miura, Therapeutic drug monitoring of imatinib for chronic myeloid leukemia patients in the chronic phase, Pharmacology 87 (2011) 241–248.

[3] R.A. Larson, B.J. Druker, F. Guilhot, S.G. O'Brien, G.J. Riviere, T. Krahnke, I. Gathmann, Y. Wang, IRIS (International Randomized Interferon vs STI571) Study Group, Imatinib pharmacokinetics and its correlation with response and safety in chronic-phase chronic myeloid leukemia: a subanalysis of the IRIS study, Blood 111 (2008) 4022–4028.

[4] S. Picard, K. Titier, G. Etienne, E. Teilhet, D. Ducint, M.A. Bernard, R. Lassalle, G. Marit, J. Reiffers, B. Begaud, N. Moore, M. Molimard, F.X. Mahon, Trough imatinib plasma levels are associated with both cytogenetic and molecular responses to standard-dose imatinib in chronic myeloid leukemia, Blood 109 (2007) 3496–3499.

[5] A. Capron, M.V. Antunes, S.C. Wagner, V.S. Mattevi, N. Vieira, R. Leite, F. Reginato, M. Capra, L. Fogliatto, P. Wallemacq, R. Linden, First report of imatinib measurement in hair: method development and preliminary evaluation of the relation between hair and plasma concentrations with therapeutic response in chronic myeloid leukemia, Clin. Chim. Acta 453 (2016) 42–47.

[6] M1. Baccarani, J. Cortes, F. Pane, D. Niederwieser, G. Saglio, J. Apperley, F. Cervantes, M. Deininger, A. Gratwohl, F. Guilhot, A. Hochhaus, M. Horowitz, T. Hughes, H. Kantarjian, R. Larson, J. Radich, B. Simonsson, R.T. Silver, J. Goldman, R. Hehlmann, European LeukemiaNet, Chronic myeloid leukemia: an update of concepts and management recommendations of European LeukemiaNet, J. Clin. Oncol. 27 (2009) 6041–6051.

[7] E.L. Kaplan, P. Meier, Nonparametric estimation from incomplete observations, J. Am. Stat. Assoc. 53 (1958) 457–481.

[8] N. Mantel, Evaluation of survival data and two new rank order statistics arising in its consideration, Cancer Chemother. Rep. 50 (1960) 163–170.

[9] P. Rousselot, H. Johnson-Ansah, F. Huguet, L. Legros, M. Escoffre-Barbe, M. Gardembas, P. Cony-Makhoul, V. Coiteux, L. Sutton, W. Abarah, C. Pouaty, J.M. Pignon, B. Choufi, S. Visanica, B. Deau, S. Bouchet, F. Guilhot, F.X. Mahon, L. Morisset, J.M. Cayuela, B. Maneglier, Personalized daily doses of imatinib by therapeutic drug monitoring Increase the rates of molecular responses in patients with chronic myeloid leukemia. Final results of the randomized OPTIM imatinib study, Blood 126 (2015) 2768.

[10] L. Noens, M.A. van Lierde, R. De Bock, G. Verhoef, P. Zachée, Z. Berneman, P. Martiat, P. Mineur, K. Van Eygen, K. MacDonald, S. De Geest, T. Albrecht, I. Abraham, Prevalence, determinants, and outcomes of nonadherence to imatinib therapy in patients with chronic myeloid leukemia: the ADAGIO study, Blood 113 (2009) 5401–5411.