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SHORT COMMUNICATION

Should therapeutic drug monitoring of the unbound fraction of imatinib and its main active metabolite *N*-desmethyl-imatinib be developed?

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Abstract

Purpose The European Society for Medical Oncology recommends therapeutic drug monitoring (TDM) for imatinib, based on total plasma concentrations in cases of sub-optimal response, failure, or adverse events. Imatinib is highly bound to alpha-1 acid glycoprotein (AGP) in the plasma. We determined the unbound plasma fraction of both imatinib and its main active metabolite (*N*-desmethyl-imatinib) in plasma from 44 patients. The objective was to quantify the inter-individual variability of the protein binding of imatinib in order to discuss the potential benefits and limits of TDM of free plasma concentrations.

Patients and methods The quantification of unbound fraction of imatinib and *N*-desmethyl-imatinib was performed using plasma ultrafiltration coupled with LC–MS/MS measurement. 60 pre-dose plasma samples were obtained at steady state within TDM in 44 chronic myeloid leukemia patients.

Results The mean unbound fractions of imatinib and *N*-desmethyl-imatinib were 2.94 and 5.10 %, respectively, with inter-individual variability (CV in %) of 57 % for imatinib and 71 % for the metabolite. For 11 patients, repeated blood sampling gave a mean intra-individual variability of 28 % for imatinib and 34 % for *N*-desmethyl-imatinib. No correlation was observed between these measured individual imatinib unbound fraction values and those obtained using an equation based on AGP levels previously proposed by Widmer et al. The mean *N*-desmethyl-imatinib/imatinib ratio was determined for both total (0.69) and unbound (1.10) concentrations, with inter-individual variabilities of 71 and 86 %, respectively.

Conclusion The large inter-individual variability for the unbound fraction of both imatinib and *N*-desmethyl-imatinib warrants further evaluation of the pharmacokinetic–pharmacodynamic relationship as a potential relevant marker of imatinib therapeutic outcomes.

Keywords Imatinib · *N*-desmethyl-imatinib · Protein binding · Unbound fraction · Therapeutic drug monitoring · Chronic myeloid leukemia

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Introduction

Imatinib is a small-molecule tyrosine kinase inhibitor that was first developed for the treatment of chronic myeloid leukemia (CML), in which disease it acts to inhibit the action of the Bcr-Abl fusion protein [6]. In addition to inhibiting ABL, imatinib is also an inhibitor of KIT and PDGFR [3]. To date, imatinib is a gold standard in the treatment of CML and gastro-intestinal stromal tumors (GIST).

Suitable drugs for therapeutic drug monitoring (TDM) programs are mainly those with large inter-individual but low intra-individual pharmacokinetic variability, with both consistent concentration–efficacy and/or concentration–toxicity relationship [16]. Such characteristics are notably met by imatinib. To date, the European Society for Medical Oncology suggests that "measuring imatinib blood concentrations may be important in all patients and is recommended in case of sub-optimal response, failure, dose-limiting toxicity or adverse events" [2]. In CML patients,

Picard et al. [18] showed that trough imatinib plasma levels were associated with the likelihood of achieving complete cytogenetic response (CCR) or major molecular response (MMR) to standard-dose imatinib, with a plasma threshold of 1,002 ng/mL. In advanced GIST, patients with lower imatinib trough plasma levels (≤1,100 ng/mL) showed a trend of lower rate of clinical response and faster time to progression [5]. Although some patients have reached or overpassed the target concentration, nonresponse or disease progression after a certain period of time may occur. This is mainly induced by mechanisms of resistance like mutations in the Bcr–Abl protein or transporters. Uptake of imatinib into the cell is predominantly an active rather than a passive uptake process, mediated by the organic cation transporter-1 (OCT-1; *SLC22A1*), whereas it is effluxed by P-glycoprotein (P-gp; *ABCB1*) and breast cancer-resistant protein (BCRP; *ABCG2*), two ATP-binding cassette transporters [20, 23]. In addition, according to the general concept developed in clinical pharmacology together with previous results specifically obtained for imatinib, we may imagine that a lower unbound plasma fraction of imatinib could be responsible for a lower pharmacodynamic effect than that expected according to total plasma concentrations. Assuming that alpha-1-acid glycoprotein (AGP) is the main binding protein for imatinib, Widmer et al. [24] developed an equation based on a patient's AGP level and the AGP dissociation constant for imatinib, K_d, to estimate the plasma unbound fraction of imatinib (f_u). They observed stronger relationships between estimated imatinib-free plasma levels with efficacy and tolerability than those based on total imatinib plasma levels. Delbado et al. [4] observed also that hematological toxicity of imatinib was more correlated with estimated unbound AUC than with total AUC.

The main objective of this study was to evaluate the inter- and intra-individual variability of unbound imatinib and *N*-desmethyl-imatinib fractions in the plasma of CML patients, using an original process [1] based on ultrafiltration (Centrifree®) coupled with UPLC–MS/MS analysis. Moreover, *N*-desmethyl-imatinib/imatinib ratios for both total and unbound concentrations with their respective inter- and intra-individual variability were explored. Finally, the proposal to use unbound imatinib and *N*-desmethyl-imatinib fractions as new markers of TDM is discussed from a theoretical point of view.

Patients and methods

Patients

Blood sampling was performed in 44 CML patients (16 women and 28 men) during their routine clinical visits, by the staff of the Oncohaematology Department of the University Hospital in Toulouse, due to sub-optimal response, failure, dose-limiting toxicity or adverse events. For each plasma sample, both total and unbound imatinib and *N*-desmethyl-imatinib concentrations, albumin and AGP levels were measured. The total imatinib concentration, as a marker of TDM, was communicated to the staff of the Oncohaematology Department to adapt the patients' drug dosage if necessary. The age of the patients ranged from 28 to 87 years with a median of 57 years. Patients received a median daily dose of 400 mg (ranged between 200 and 800 mg).

Determination of imatinib and *N*-desmethyl-imatinib total and unbound plasma concentrations

Both imatinib and *N*-desmethyl-imatinib total and unbound trough concentrations were determined in 60 plasma samples (44 patients) according to a previously published method [1]. Briefly, 200 µL of patient's plasma was added to the sample reservoir of the Centrifree® YM-30 (Millipore) unit after thawing plasma samples at ambient temperature, and 200 µL of blank plasma was added in the collection tube of the ultrafiltration device. Tubes were then centrifuged for 40 min at 2,000*g* and 20 C. The solution (ultrafiltrate mixed with plasma) collected in the filtration collection cup was analyzed using a validated UPLC–MS/MS method with a limit of quantification of 10 ng/mL for imatinib and 20 ng/mL for *N*-desmethyl-imatinib. Respective unbound fractions (f_u and $f_{u,m}$ expressed in %) were calculated by dividing unbound concentrations by corresponding total concentrations. Inter- and intra-individual variabilities were expressed as the coefficient of variation (CV) calculated by dividing the standard deviation by the corresponding mean and were expressed in percentage.

Alpha-1-acid glycoprotein and albumin assays

Alpha-1-acid glycoprotein and albumin methods used on the Dimension® clinical chemistry system are in vitro diagnostic tests intended for the quantitative determination of albumin and of alpha-1-acid glycoprotein, in human serum and plasma.

The albumin method is an adaptation of the bromocresol purple (BCP) dye-binding method. The amount of albumin–BCP complex is directly proportional to the albumin concentration. The determination of alpha-1-acid glycoprotein is based on the turbidimetric-specific reaction which occurs between the anti-alpha-1-acid glycoprotein polyclonal antiserum and its corresponding antigen in optimal conditions and in the presence of polyethylene glycol polymer (PEG). The turbidity of the immuno-complex is proportional to the

concentration of alpha-1-acid glycoprotein. The analytical measurement range for AGP is 0.07–2.8 g/L, and 6–80 g/L for albumin. The reference values are 0.5–1.4 g/L for AGP and 34–50 g/L for albumin.

Results

Mean (range) unbound fractions of imatinib and *N*-desmethyl-imatinib were 2.94 % (1.03–9.79 %) and 5.10 (0.73–16.34 %), respectively (Table 1). The CV for inter-individual variability was 57 % for imatinib, and 71 % for *N*-desmethyl-imatinib unbound fraction. For 11 patients, repeated blood sampling (2–3 samples *per* patient) was performed for TDM for a period of time ranging from 3 to 254 days. The mean value of the CV (range) for intra-individual variability of the unbound fraction was 28 % (9–72 %) for imatinib and 34 % (8–54 %) for *N*-desmethyl-imatinib.

For the same patients, the mean (range) unbound fraction of imatinib estimated from the total concentration and AGP level, using the Widmer's equation [24] updated recently for K_d value [13] ($C_u = \frac{C_{tot} - K_d - L \times AGP + \sqrt{(C_{tot} - K_d - L \times AGP)^2 + 4 \times K_d \times C_{tot}}}{2}$; with $K_d = 0.319$ mg/L; $L = 11.7$), was 3.10 % (1.18–5.21 %). This value is consistent with the above-measured f_u values, but no correlation was observed between individual estimated and measured values (slope = 0.0448 and $R^2 = 0.0008$). Moreover, no correlation was observed between either f_u or $f_{u,m}$ and AGP (f_u: slope = 0.0664 and $R^2 = 0.00031$; $f_{u,m}$: slope = 2.2019 and $R^2 = 0.09129$) or albumin (f_u: slope = 0.0638 and $R^2 = 0.02558$; $f_{u,m}$: slope = 0.0001 and $R^2 = 0.00000006$).

Mean (range) *N*-desmethyl-imatinib/imatinib ratio was 0.69 (0.19–2.81) for total concentrations, and 1.10 (0.26–5.41) for unbound concentrations (Table 1), with an inter-individual variability of 71 and 86 %, and an intra-individual variability of 43 % (5–95 %) and 29 % (6–87 %), respectively. No correlation was observed between unbound and total *N*-desmethyl-imatinib/imatinib ratios.

Discussion

Applying the original procedure validated by Arellano et al. [1], unbound fractions of imatinib were determined in CML patients. The unbound imatinib fraction (2.94 %) agrees with the mean values, determined by ultrafiltration or equilibrium dialysis, reported by Smith [21] (5.0 % in healthy adult volunteers), Kretz [14] (5.0 % in healthy humans), Reardon [19] (4.9 % in patients with recurrent glioblastoma multiforme), Gibbons [11] (5.5 % in adult patients with advanced solid tumors and varying renal function) and Streit [22] (5.0 and 4.5 % in CML and GIST patients, respectively). The mean determined value of f_u was similar to that estimated by using the Widmer equation [24] and a K_d value of 0.319 mg/L [13] (3.10 %), but no correlation was observed between measured and estimated individual values. The lack of correlation between the observed imatinib f_u and Widmer's estimations based on AGP levels pointed out the lack of correlation with AGP levels that we also observed between f_u and individual AGP levels. This may be explained, at least partially, by the limited dispersion of the AGP levels of these patients; 33/44 had AGP level within normal range (i.e., 0.5–1.4 g/L). Moreover, AGP shows genetic polymorphism and the binding of imatinib to the two main genetic variants (F1-S and A) is very different [8] with high affinity-specific binding of imatinib to the F1-S genetic variant. This is the dominant component, and in some pathological conditions, the concentration of this fraction can even be selectively elevated. However, AGP polymorphism was not explored in our population. On the other hand, the absence of correlation between plasma albumin levels and fu was not surprising as the binding affinity of imatinib to human serum albumin is low [8].

N-desmethyl-imatinib, the primary metabolite of imatinib, was also explored as this molecule has been reported

Table 1 Imatinib and *N*-desmethyl-imatinib total and unbound concentrations, unbound fractions, *N*-desmethyl-imatinib/imatinib concentrations ratios, and proteins (AGL, albumin) levels in 44 patients

	Mean	CV (%)	Min	Max
Imatinib total concentration (ng/mL)	1,150	89	180	6,100
Imatinib unbound concentration (ng/mL)	30.9	81	2.8	130.4
Imatinib f_u (%)	2.94	57	1.03	9.79
N-desmethyl-imatinib total concentration (ng/mL)	765	121	91	5,365
N-desmethyl-imatinib unbound concentration (ng/mL)	21.4	28	14.6	38.3
N-desmethyl-imatinib f_u (%)	5.10	71	0.73	16.34
Total conc. *N*-desmethyl-imatinib/imatinib ratio	0.69	71	0.19	2.81
Unbound conc. *N*-desmethyl-imatinib/imatinib ratio	1.10	86	0.26	5.41
AGP plasma level (g/L)	1.08	43	0.55	2.97
Albumin plasma level (g/L)	42.7	10	34.0	51.4

to be pharmacologically active before undergoing a phase II metabolic pathway (glucuronidation) [12]. Mlejnek et al. [17] provided evidence that *N*-desmethyl-imatinib was able to inhibit cell proliferation and induced apoptosis in sensitive human chronic myelogenous leukemia K562 cells, although its effect was approximately three to four times lower than that of imatinib in the same cell line. Although little is known about its cellular influx, the same authors observed that *N*-desmethyl-imatinib was an excellent substrate for P-gp.

The mean value we obtained for the total plasma concentrations *N*-desmethyl-imatinib/imatinib ratio (i.e., 0.69) was larger than the values previously reported (around 0.25 [4, 22]), but consistent with that recently observed by Eechoute et al. [7] for *N*-desmethyl-imatinib/imatinib AUC ratio (i.e., 0.72). The high inter-individual variability (the ratio varied 15-fold, from 0.19 to 2.81 in our study) may explain in part this inconstancy between studies. This large inter-individual variability is not surprising as imatinib metabolism by CYP3A4 is subject to individual differences, as well as drug–drug and drug–diet interactions [20]. Clearance can also be altered by genetic and environmentally changes in imatinib efflux mediated by transporters (P-gp, BCRP) [6]. Moreover, unpredictable compliance is the usual cause of variability in the ratio. Poor compliance with treatment has repeatedly been documented to occur despite the gravity of the pathology. The changes in drug to metabolite ratios in the same patient with time after dose [21] suggest that these ratios may be useful to detect noncompliant patients who ingest imatinib only before having blood samples drawn.

From a theoretical point of view, the impact of large inter-individual variability that we observed for both f_u and $f_{u,m}$ on pharmacokinetic–pharmacodynamic (PK-PD) relationships should be considered with the respective affinity of these two compounds to plasma proteins and the uptake transporters (Fig. 1). Indeed, if binding affinity of imatinib for OCT-1 is much higher than for plasma proteins, the drug may be displaced from the plasma protein sites of fixation within the tissues where the transporters are expressed. In this case, PK-PD relationships would not be improved by taking into account individual f_u and $f_{u,m}$ values. However, several preclinical experiments indicate that the binding of imatinib on plasma proteins should be a limiting factor for its diffusion within the cells. Gambacorti-Pesserini et al. [9] showed in vitro that addition of AGP (2 g/L) increased imatinib IC_{50} on Bcr-Abl$^+$ KU812 cells from 0.05 μM to >3.0 μM. Larghero et al. [15] also showed that addition of AGP to culture medium reduced the pharmacological activity of imatinib on K562 Bcr–Abl-positive cells. In a similar way, Gambacorti-Pesserini et al. [10] evaluated the biological effect of AGP on leukemia cells isolated from patients: AGP at 1.5 g/L decreased the intracellular concentration of imatinib to <10 % of control and almost completely abrogated the pharmacological activity of imatinib. These results suggest that the more the patient presents a low plasma unbound fraction, the more the imatinib gets trapped outside the leukemia cell and the more the treatment is inefficient mimicking resistance phenomena.

In the case of *N*-desmethyl-imatinib, it is difficult to date to discuss the relevance of the unbound fraction. However, as *N*-desmethyl-imatinib is the active metabolite of imatinib, it seems logical that the association of imatinib and *N*-desmethyl-imatinib unbound fractions could improve dose adjustment compared with imatinib alone, as is also the

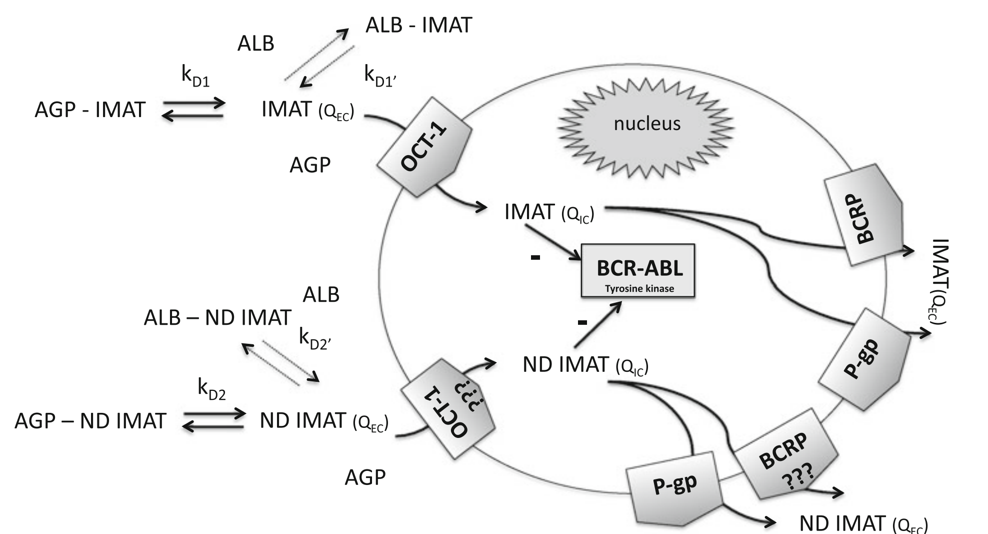

Fig. 1 Factors affecting intracellular imatinib and *N*-desmethyl-imatinib concentrations in leukemia cells

case for other drugs like clomipramine (antidepressant drug) and its active metabolite *N*-desmethyl-clomipramine, where the sum of the respective total plasma concentrations is used for TDM. That is emphasized by the wide variability of the *N*-desmethyl-imatinib/imatinib ratios that we observed (71 and 86 % for total and unbound concentrations, respectively) without correlation between total and unbound concentrations ratios pointing out the fact that unbound *N*-desmethyl-imatinib measurement may provide additional information with clinical relevance.

Although plasma ultrafiltration associated with LC–MS/MS analysis is a time-consuming process, both unbound imatinib and *N*-desmethyl-imatinib concentrations have to be determined and cannot be estimated based only on AGP. Measurement of these concentrations and of their respective unbound fraction provided useful information on intra- and inter-individual variability, suggesting that measurement of unbound fraction for imatinib could improve patients' drug dosage adjustment and the ability to predict individual responses to imatinib therapy. Prospective pharmacokinetic studies should be performed to confirm the interest of determination of imatinib and *N*-desmethyl-imatinib unbound concentrations.

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Conflict of interest None.

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