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ORIGINAL ARTICLE

CYP2D6 and *CYP2C8* pharmacogenetics and pharmacological interactions to predict imatinib plasmatic exposure in GIST patients

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Aims: Patients on treatment with oral fixed dose imatinib are frequently under- or overexposed to the drug. We investigated the association between the gene activity score (GAS) of imatinib-metabolizing cytochromes (*CYP3A4*, *CYP3A5*, *CYP2D6*, *CYP2C9*, *CYP2C19*, *CYP2C8*) and imatinib and nor-imatinib exposure. We also investigated the impact of concurrent drug–drug-interactions (DDIs) on the association between GAS and imatinib exposure.

Methods: Serial plasma samples were collected from 33 GIST patients treated with imatinib 400 mg daily within a prospective clinical trial. Imatinib and nor-imatinib C_{trough} were quantified by liquid chromatography with tandem mass spectrometry (LC-MS/MS). Genetic polymorphisms with a functional impact on imatinib-metabolizing cytochromes were identified and a GAS was calculated for each gene. A DDI-adjusted GAS was also generated.

Results: Imatinib and nor-imatinib C_{trough} were measured in 161 plasma samples. *CYP2D6* GAS and metabolizer status based on genotype were associated with imatinib and (imatinib + nor-imatinib) C_{trough}. *CYP2D6* poor and intermediate metabolizers were predicted to have a lower nor-imatinib/imatinib metabolic ratio than normal metabolizers (0.197 and 0.193 *vs.* 0.247, $P = .0205$), whereas *CYP2C8*3* carriers had a higher ratio than *CYP2C8*1/*1* patients (0.263 *vs.* 0.201, $P = .0220$). CYP2C9 metabolizer status was inversely related to the metabolic ratio with an effect probably driven by the linkage disequilibrium between *CYP2C9*2* and *CYP2C8*3*. The *CYP2D6* DDI-adjusted GAS was still predictive of imatinib exposure.

Conclusions: These findings highlight that *CYP2D6* plays a major role in imatinib pharmacokinetics, but other players (i.e., *CYP2C8*) may influence imatinib exposure. These findings could drive the selection of patients more susceptible to imatinib

under- or overexposure who could be candidates for personalized treatment and intensified monitoring strategies.

KEYWORDS
CYP2C8, *CYP2D6*, GIST, imatinib, pharmacogenetics

1 | INTRODUCTION

In the era of precision medicine, the dose and schedule of targeted oral anticancer drugs are still based on the one-size-fits-all paradigm, with dose adjustments driven by the onset of toxicity or lack of efficacy. The majority of gastrointestinal stromal tumour (GIST) patients treated with **imatinib** present a drug plasma level outside the recommended range for a safe and efficacious treatment.[1,2] Specifically, an imatinib C_{trough} of 1100 ng/mL at the steady state was associated with higher rates of objective response and lower risk of disease progression.[1,3]

Imatinib is administered at a fixed starting dose of 400 mg daily, although a dose escalation to 800 mg daily is recommended for most patients experiencing disease progression. Pharmacokinetic studies have highlighted several variables affecting imatinib exposure, including body weight, granulocyte count, as well as AGP, albumin and haemoglobin levels.[4,5]

Interindividual variability in the efficiency of imatinib metabolism may also impact its pharmacokinetics. The metabolism of imatinib relies mainly on the cytochrome P450 isoenzyme **CYP3A4**, which mediates the conversion of imatinib to its active metabolite N-desmethylimatinib or nor-imatinib, while other enzymatic players, such as CYP3A5, **CYP2C8**, **CYP2C9**, CYP2C19 and **CYP2D6** play a minor role. The pharmacogenetic background of the patients for cytochrome encoding genes could affect the efficiency of the drug metabolism and impact its plasmatic exposure. Although there is evidence that genetic polymorphisms in cytochrome encoding genes could predict the plasmatic exposure to imatinib,[6] pharmacogenetic research has yielded conflicting results up to now.[7]

Cytochrome expression is also highly modulated by the pharmacological interactions, and this is particularly relevant in GIST patients that can receive imatinib for several years. Moreover, oncology patients are frequently treated with a combination polypharmacy that might strongly affect drug metabolism and exposure.[8]

The combination of such potentially harmful issues as gene–drug interactions (DGI) and drug–drug interactions (DDI) are hardly considered in clinical practice.[9] Taking drug–drug–gene interactions (DDGIs) into account provides an opportunity to study complex interactions between DGIs and DDIs. This integrated approach should allow taking into consideration the phenomenon of phenoconversion, which describes the transient shift from the genotype-based expected phenotype to the clinical phenotype based on the interaction between genetic factors and concomitantly administered agents (i.e., drugs, smoking, food, etc.).[10] Phenoconversion is a dynamic phenomenon and can also explain intra-patient variability in plasmatic drug exposure over the course of treatment, due to the introduction of new treatments or lifestyle habits.

In this work, the association between the gene activity score (GAS) of imatinib-metabolizing cytochromes (*CYP3A4*, *CYP3A5*, *CYP2D6*, *CYP2C9*, *CYP2C19*, *CYP2C8*) and the plasma C_{trough} of imatinib and its active metabolite nor-imatinib was investigated in a prospective bulk of plasma samples collected from imatinib-receiving GIST patients enrolled in a prospective clinical trial. We further investigated the effect of the DDIs on this association and how a DDI-adjusted GAS might improve the prediction of the imatinib and its metabolite plasmatic exposure (C_{trough}).

What is already known about this subject

- Imatinib plasmatic exposure affects its efficacy and safety in GIST patients.
- Pharmacogenetic variants on imatinib-metabolizing CYPs and drug–drug interactions (DDIs) can affect imatinib metabolism.
- Only limited knowledge is available concerning the concurrent effect of imatinib pharmacogenetics and DDIs in GIST patients.

What this study adds

- The concomitant effect of the gene activity score of imatinib-metabolizing CYP and of DDIs was investigated for the first time in a prospective cohort of GIST patients receiving imatinib standard dose.
- The *CYP2D6* activity score was shown to predict imatinib exposure (C_{trough}) also after adjustment for DDIs.
- *CYP2D6* phenotype and *CYP2C8*3* genotype were related to nor-imatinib/imatinib metabolic ratio.
- CYP2C9 phenotype was inversely related to nor-imatinib/imatinib metabolic ratio. This paradoxical effect might be driven by the existing linkage disequilibrium between *CYP2C9*2* decreased activity allele and *CYP2C8*3* increased activity allele.

2 | METHODS

2.1 | Patient selection

Consecutive GIST patients were prospectively enrolled in the framework of a clinical trial coordinated by IRCCS Centro di Riferimento Oncologico of Aviano (Italy). The clinical trial was approved by the local ethical committee and registered by the Italian Medicines Agency (AIFA) (EudraCT number 2017-002437-36) and was conducted according to the Declaration of Helsinki. The protocol had the primary aim to assess the feasibility of a routine therapeutic drug monitoring (TDM) of imatinib and circulating tumour DNA analysis in serial blood samples from GIST patients. Eligibility criteria were as follows: (i) histologically confirmed GIST, (ii) treatment with imatinib > 90 days prior to study entry, regardless of the administration setting, (iii) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, (iv) adequate liver, renal and bone marrow function, (v) age ≥18, (vi) capability of attending scheduled medical check-ups regularly, and (vii) signed informed consent.

For the purposes of the presented sub-study, patients who met specific additional requirements were selected: (i) administration of imatinib 400 mg daily dose, (ii) availability of detailed information on co-administered drugs, and (iii) concentration of imatinib and nor-imatinib above the lower limit of quantification (LLOQ; i.e., 30 ng/mL for imatinib and 6 ng/mL for nor-imatinib).

2.2 | Blood collection and genomic DNA extraction

Fifteen millilitres of blood were routinely collected as per protocol methodology in K_2-EDTA containing tubes at the time of regular medical check-ups, every 3–6 months. Plasma was separated by means of centrifugation and stored at −80°C until imatinib and nor-imatinib quantification. Genomic DNA was extracted from the harvested buffy coat by means of the GeneJET Whole Blood Genomic DNA Purification Mini kit (Thermo Fisher Scientific, Wilmington, DE, USA) and quantified by Quantus Fluorometer (Promega, Madison, WI, USA). Genomic DNA was stored at 4°C.

2.3 | Genotyping and gene activity score calculation

A panel of 33 targeted SNPs was assessed in *CYP3A4*, *CYP3A5*, *CYP2D6*, *CYP2C9* and *CYP2C19* using validated KASP genotyping assays (LGC Genomics, Novato, CA, USA) using the semi-automated SNPline PCR Genotyping System (LGC Genomics) and the Applied Biosystems™ 7500 Real-Time PCR system (Applied Biosystem, Foster City, CA, USA). A detailed list of the variants analysed is reported in Table S1. *CYP2C8* was analysed by means of targeted next-generation sequencing (NGS). Sequencing libraries were prepared starting from 100 ng of genomic DNA using a custom hybridization-based NimbleGen SeqCap EZ Choice Library (Roche, Inc., Madison, WI, USA) targeting the untranslated regions (UTRs) and the coding sequence of 60 cancer-related genes, according to the NimbleGen SeqCap EZ Library SR User's Guide v3.0 (Roche, Inc., Madison, WI, USA) (see Supplementary Methods).

Each allele was assigned a numerical value that represents its predicted activity, i.e., the activity score, according to information reported on specific 'Allele Functionality Table' on PharmGKB and to published literature.[11] Detailed information on activity score calculation for individual CYPs is reported in the Supplementary Methods.

The GAS was calculated for each CYP in each patient by summing the activity scores of the individual alleles comprising the diplotype. The GAS and the corresponding predicted metabolic phenotype for each observed diplotype are summarized in Table S2.

2.4 | DDI collection and DDI-adjusted GAS calculation

At each scheduled blood sampling, patients were asked to complete a questionnaire indicating what medications they were taking, when they started taking the medications and whether treatment had been interrupted in the last 7 days. They were also asked about their smoking habits. Moreover, patients' clinical records were interrogated to integrate the information collected through direct questioning. Only medications taken for at least 7 days prior to blood collection were considered for analysis of potential interactions. Two different electronic databases were systematically queried to assess the effects of each concomitant drug on imatinib metabolizing CYPs, i.e., the Flockhart Interaction Table, and the Food and Drug Administration (FDA) website.[12,13] Moreover, the summary of product characteristics of Gleevec,[14] and of individual comedications was interrogated to check for additional information. Each drug was classified as a strong inducer, moderate/mild inducer, not interacting, moderate/mild inhibitor or strong inhibitor with respect to every analysed CYP.

The DDI-adjusted GAS was calculated in each patient, for each CYP, at every available sampling time considering the concomitant intake of interacting drugs registered at that time point. Each patient was also assigned a metabolizer phenotype according to available pharmacogenetic guidelines by the Clinical Pharmacogenetics Implementation Consortium (CPIC) and/or the Dutch Pharmacogenetics Working Group (DPWG) (Table S2), The DDI-adjusted GAS was calculated by multiplying the GAS by 0 (strong inhibitor), by 0.5 (moderate/mild inhibitor), by 1.5 (moderate/mild inducer), and by 2.0 (strong inducer), as previously reported.[15] Samples where the concomitance of two or more DDIs was reported were excluded from the analysis.

2.5 | LC–MS/MS quantification of imatinib and nor-imatinib plasma concentrations

Quantification of imatinib and nor-imatinib was performed using a liquid chromatography with tandem mass spectrometry (LC-MS/MS)

instrument consisting of a Prominence LC-20 AD UFLC XR (Shimadzu, Tokyo, Japan) and an API 4000 QTrap mass spectrometer (SCIEX, Framingham, MA, USA). Imatinib and nor-imatinib were quantified after simple protein precipitation using methanol as an extraction method. The analytes were separated on a Synergi Fusion RP C18 chromatography column 4 μm, 50 × 2.0 mm coupled to a C18 precolumn (Phenomenex, Torrence, CA, USA). Elution was performed in gradient mode chromatography. The mass spectrometer was equipped with an electrospray ionization (ESI) source interface and was operated in positive ion mode. The biological samples were analysed in selected reaction monitoring mode. Quantifications were performed using the following transitions: *m/z* 494.4 > 394.2 for imatinib, *m/z* 480.4 > 394.2 for nor-imatinib and *m/z* 502.4 > 394.2 for imatinib-D8, employed as an internal standard. The developed method was validated according to FDA and European Medicines Agency (EMA) guidelines for validation of bioanalytical methods, evaluating linearity, recovery, limit of detection, limit of quantification, matrix effect, inter- and intra-day precision and accuracy, selectivity, stability and reproducibility.

To ensure homogeneous quantification of imatinib and nor-imatinib C_{trough}, blood samples were preferably collected 24 h after the last imatinib administration. If imatinib had not been administered exactly 24 h prior to blood collection, the following formula, previously validated by Wang et al.,[16] was used to extrapolate imatinib and nor-imatinib C_{trough}:

$$C_{trough} = C * 0.5^{\frac{24-T}{T_{1/2}}}$$

where C = measured drug concentration, T = hours from the last drug administration, and $T_{1/2}$ = drug plasma half-life (imatinib 18 h, nor-imatinib 40 h).

The samples collected up to 5 h or after 35 h from the last imatinib administration were excluded from the analysis as they were outside the algorithm's range of linearity.

2.6 | Statistical analysis

Chi-squared analysis was used to test for genotype deviation from Hardy–Weinberg equilibrium. The metabolic ratio was calculated as [nor-imatinib C_{trough} (ng/mL)/imatinib C_{trough} (ng/mL)]. Considering the hierarchical organization of the data with blood samples nested within patients, a multilevel regression model was implemented to assess the effect of imatinib-metabolizing CYPs and comedications on imatinib and nor-imatinib C_{trough} concentrations. Sample-specific data (e.g., C_{trough} concentration, age at sampling, comedication) were included in the first level, while patient-specific characteristics (e.g., CYPs, gender) were included in the second level. Positive β regression coefficients indicate an increase in C_{trough} concentrations whereas negative coefficients indicate a decrease in C_{trough} concentrations. For each patient, the median nor-imatinib/imatinib metabolic ratio and C_{trough} were considered for a descriptive analysis according to genotypes and phenotypes by non-parametric Mann–Whitney/Kruskal–Wallis test. All statistical analyses and data visualizations were performed using SAS 9.4 and R software 3.6. Statistical significance was claimed for $P < .05$.

2.7 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.[17]

3 | RESULTS

3.1 | Study population

Between February 2018 and January 2022, a total of 209 plasma samples from 49 consecutive patients receiving imatinib were enrolled in the main clinical trial (2017-002437-369). Of these, 163 plasma samples from 33 patients who met the inclusion criteria for the present study were considered (median: four samples/patient, range: 1–11).

All patients were Caucasian. The detailed characteristics of the eligible patients are shown in Table 1.

TABLE 1 Patient characteristics of 33 GIST patients

Patient characteristic	*n*	%
Gender		
Male	16	48.5
Female	17	51.5
Age at enrolment		
Median (range)	66 (35–83)	
Tumour site		
Stomach	15	45.5
Intestinal	13	39.4
Other[a]	5	15.1
Imatinib setting at enrolment		
Adjuvant	9	27.3
First line	24	72.7
Blood samples collected		
≤3	16	48.5
3–7	6	18.2
≥7	11	33.3
Comedications	**Number of samples**	
0	27	16.6
1–3	93	57.1
4–6	32	19.6
≥	7	4.3

[a]Abdominal, pelvic region and peritoneum.

3.2 | Imatinib exposure and demographic features

Imatinib and nor-imatinib were successfully quantified in 161 of the 163 (98.8%) plasma samples, as two samples from the same patient (#IM20) were below the LLOQ. Imatinib C_{trough} levels ranged from a minimum of 264.1 ng/mL to a maximum of 3494.6 ng/mL, with a median of 908.4 ng/mL (interquartile range [IQR]: 685.1 ng/mL – 1210.3 ng/mL). Likewise, (imatinib + nor-imatinib) C_{trough} levels ranged from a minimum of 349.5 ng/mL to a maximum of 4049.6 ng/mL, with a median of 1116.3 ng/mL (IQR: 839.4 ng/mL – 1495.9 ng/mL). Intra-patient and interpatient variability were relatively wide. The mean intra-patient variability (coefficient of variation) was 24.1% for imatinib and 23.0% for (nor-imatinib + imatinib), while the mean inter-patient variability was 53.2% for imatinib and 51.3% for (nor-imatinib + imatinib).

In the univariate analysis, higher imatinib and (imatinib + nor-imatinib) plasma C_{trough} levels were significantly associated with patient age ≥75 years ($P = .0023$ and $P = .0020$, respectively), while no significant association was observed between imatinib or (imatinib + nor-imatinib) C_{trough}, body mass index (BMI) and tobacco smoking. Despite not being statistically significant, an increasing trend for imatinib (+32.8%) and (imatinib + nor-imatinib) (+34.3%) C_{trough} was observed in female patients over male (Table 2).

3.3 | Imatinib exposure and *CYP* genotype/phenotype

All 33 patients were successfully genotyped for the candidate variants. Genotype distribution did not deviate significantly from the Hardy–Weinberg equilibrium ($P > .05$). Detailed information on the genotype distribution is reported in Table S3.

The relationship between the calculated GAS of every CYP and imatinib and (imatinib + nor-imatinib) exposure was investigated by applying a multilevel linear regression model adjusted for gender and age at sampling (Table 3). *CYP2D6* GAS accounted for most of the interindividual variability in imatinib ($P = .0074$) and (imatinib + nor-imatinib) ($P = .0082$) exposure, with an estimated decrease of 369.0 ng/mL imatinib and of 426.7 ng/mL (imatinib + nor-imatinib) for each unit of *CYP2D6* GAS gained.

The GAS of other CYPs was not significantly associated with imatinib and (imatinib + nor-imatinib) C_{trough} ($P > .05$). An additional

TABLE 3 Association[a] between gene activity score (GAS) and plasma trough level of imatinib, imatinib + nor-imatinib and nor-imatinib/imatinib in 33 GIST patients undergoing treatment with imatinib 400 mg/die

	Imatinib		Imatinib + nor-imatinib	
	β	*P*	*β*	*P*
CYP3A4	*−828.3*	0.4290	*−1066.5*	0.3825
CYP3A5	*369.6*	0.3203	*390.7*	0.3687
CYP2C8	*−213.8*	0.2977	*−208.0*	0.3878
CYP2D6	*−369.0*	0.0074	*−426.7*	0.0082
CYP2C9	*−137.7*	0.5243	*−202.6*	0.4226
CYP2C19	*−165.9*	0.2885	*−203.2*	0.2663

[a]Estimated on 161 blood samples using multilevel regression model, adjusting for gender and age at sampling.

TABLE 2 Median imatinib and (imatinib + nor-imatinib) plasma C_{trough} according to patient characteristics

	n	(%)	Imatinib (ng/mL)	Imatinib + nor-imatinib (ng/mL)
All patients	**33**		**839.2**	**1012.8**
Gender				
Male	16	(48.5)	738.2	880.7
Female	17	(51.5)	980.0	1182.8
			$P = .0975$	$P = .0838$
Current tobacco user				
No	20	(60.6)	816.3	974.9
Yes	5	(15.2)	735.6	859.5
Unknown	8	(24.2)	1028.0	1236.3
			$P = .2727$	$P = .2210$
Body mass index				
<25 kg m^{-2}	21	(63.6)	797.6	1012.8
≥25 kg m^{-2}	12	(36.4)	841.2	1005.9
			$P = 1.0000$	$P = .9403$
All samples	**161**		**912.3**	**1177.7**
<60	52	(32.3)	865.3	1010.4
60–74	67	(41.6)	848.8	1046.7
≥75	42	(26.1)	1203.1	1427.5
			$P = .0023$	$P = .0020$

descriptive analysis was performed to show the effect of each phenotype or genotype (if the phenotype was not available) on imatinib plasmatic exposure. The analysis confirmed the major role of *CYP2D6* genotype-predicted phenotype on the prediction of imatinib and (imatinib + nor-imatinib) $C_{through}$ ($P = .0108$ and $P = .0189$, respectively by univariate Mann–Whitney/Kruskal–Wallis test) (Table S4).

3.4 | Imatinib metabolic ratio and *CYP* genotype/phenotype

The effect of all cytochrome phenotype or genotype (for *CYP2C8*) on nor-imatinib/imatinib metabolic ratio was investigated in a per patient analysis. Per patient average nor-imatinib/imatinib metabolic ratio was 0.22 (range: 0.15–0.56), with an interpatient variability of 34.1% (coefficient of variation). Nor-imatinib/imatinib metabolic ratio was significantly higher in *CYP2C8*1/*3*-increased activity genotype with respect to *CYP2C8*1/*1* carriers (Figure 1A). In *CYP2C8*1/*1* ($n = 26$), the median metabolic ratio was 0.201, while in *CYP2C8*1/*3* ($n = 7$) it was 0.263 ($P = .0220$). A similar trend was observed for *CYP2D6* metabolic phenotype, showing that normal metabolizers (NM, $n = 17$) presented a median metabolic ratio of 0.247, higher than that of intermediate (IM) or poor (PM) metabolizers (0.193 and 0.197, respectively, $P = .0205$) (Figure 1C). *CYP2C9* phenotype was associated with nor-imatinib/imatinib metabolic ratio with an opposite trend, with a median for NM (0.198) significantly lower than IM (0.250) ($P = .0290$) (Figure 1B) *CYP3A4*, *CYP3A5* and *CYP2C19* phenotypes did not correlate with the imatinib metabolic ratio (data not shown).

3.5 | DDIs and DDI-adjusted GAS

A total of 48 comedications were identified through patient interviews and review of clinical records. Twenty-one out of 33 (63.6%) patients were administered with at least one comedication in the course of imatinib intake, while the remaining 12 patients (36.4%) did not report any concurrent treatment. Five out of 33 (15.2%) patients were treated with more than four and up to nine drugs while on imatinib.

The most frequently prescribed drugs were **cholecalciferol** and **hydrochlorothiazide**, which were registered in four out of 33 (12.1%) patients, followed by **pantoprazole**, **aspirin**, **ramipril**, **pravastatin**, **levothyroxine** and **ibuprofen**, which were reported by three out of 33 (9.1%) patients. A detailed list of the administered comedications in the course of monitoring, their class and the number of cotreated patients are reported in Table S5.

Of the 48 registered drugs, eight were classified as potentially interacting with the pharmacokinetics of imatinib because of an inhibitory or inducing effect on imatinib metabolizing CYPs. Drugs that were classified as interacting are: **acyclovir**, **amlodipine**, **carbamazepine**, **ciprofloxacin**, **escitalopram**, **esomeprazole**, **omeprazole** and pantoprazole. Their predicted interaction with imatinib-metabolizing CYPs is reported in Table S6. Nine out of 33 (27.3%) patients were treated with at least one interacting drug while on surveillance. From these patients, a total of 30 plasma samples were taken in the course of administration with DDIs, and a DDI-adjusted GAS was attributed to each time sample collected in the course of DDI intake. Of the nine patients who underwent DDGIs, six (66.7%) changed their DDI-adjusted GAS over the course of treatment as they have been treated with different interacting drugs over time. The remaining three (33.3%) patients maintained the same DDI-adjusted GAS as they were treated with chronic

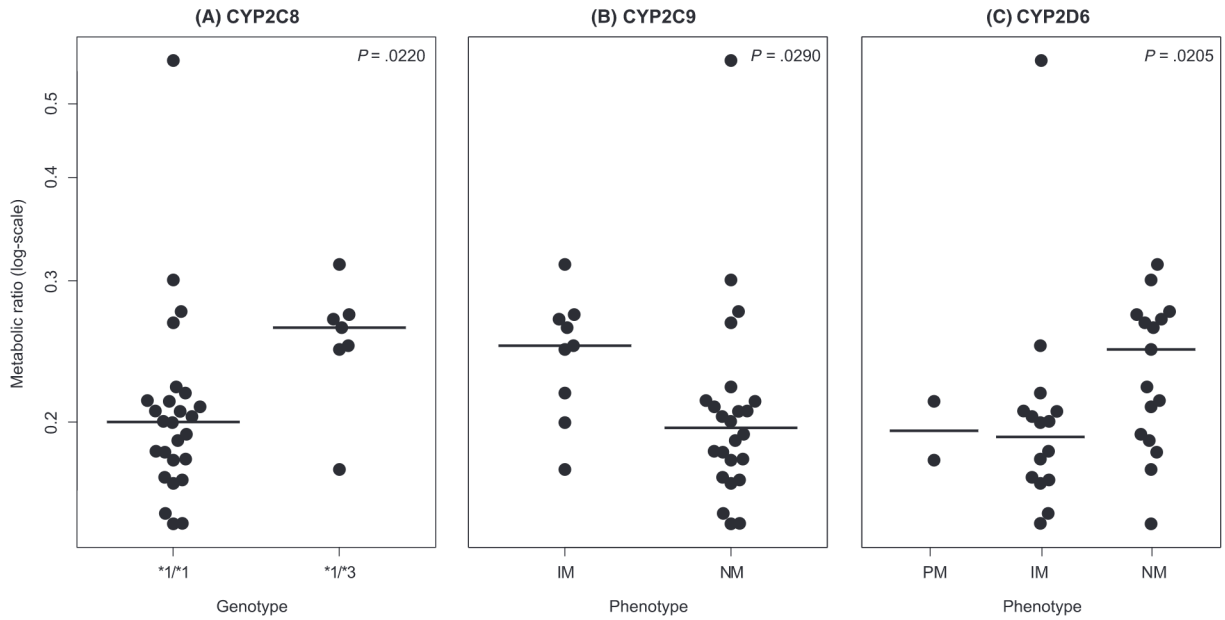

FIGURE 1 Influence of *CYP2C8*3*, *CYP2D6* and *CYP2C9* phenotype on nor-imatinib/imatinib metabolic ratio. Median nor-imatinib/imatinib metabolic ratio in 33 GIST patients according to the *CYP2C8* (1A), *CYP2C9* (1B) and *CYP2D6* (1C) genotype or phenotype. Each dot represents a patient. *P*-value is calculated by Kruskal–Wallis test.

therapies that were not changed or discontinued during the TDM monitoring timeframe.

3.6 | DDI-adjusted GAS and imatinib exposure

The results presented below refer to a per-sample analysis. The multilevel regression model was implemented to evaluate the effect of the DDI-adjusted GAS of each CYP on imatinib and (imatinib + nor-imatinib) C_{trough} (Table 4). The DDI-adjusted GAS of *CYP2D6* was found to negatively correlate with imatinib ($P = .0085$) and (imatinib + nor-imatinib) C_{trough} ($P = .0094$), with an estimated decrease of 360.0 ng/mL for imatinib, and of 415.5 ng/mL for (imatinib + nor-imatinib) for each unit of *CYP2D6* DDI-adjusted GAS gained.

Stratification of samples by DDI-adjusted GAS of *CYP2D6* did not improve the prediction of the metabolic phenotype with respect to the stratification based solely on *CYP2D6* GAS. Indeed, it was observed that imatinib and (imatinib + nor-imatinib) C_{trough} were increased by 2.5% (β-value from −369.0 to −360.0) and 2.6% (β-value from −426.7 to −415.5), respectively, when switching from GAS to DDI-adjusted GAS stratification. The DDI-adjusted GAS of the other CYPs had no significant effect on the C_{trough} of imatinib and (imatinib + nor-imatinib) ($P > .05$).

Despite the fact that the model failed to support the impact of DDI-adjusted GAS on imatinib exposure, a clinically relevant interaction between imatinib and carbamazepine was identified in one patient. The patient was a normal metabolizer for all the analysed CYPs, thus excluding the impact of gene–drug interactions. Carbamazepine is classified as a strong inducer of CYP3A4/5 and as a weak inducer of CYP2C9, whose administration must be carefully evaluated in imatinib-receiving patients according to Gleevec's label. The patient (#IM10) was chronically treated with 400 mg first line imatinib and with carbamazepine 200 mg daily for epilepsy. In the course of monitoring, the average imatinib and (imatinib + nor-imatinib) C_{trough} of the four samples collected were 315.9 ng/mL and 493.2 ng/mL, respectively, and accounted for the lower drug's exposure in the study cohort. The patient presented a metabolic ratio of 0.56 (outlier in Figure 1A). A steep increase of imatinib and (imatinib + nor-imatinib) C_{trough} up to 4297 ng/mL and 6172 ng/mL, respectively, was registered after the switch from carbamazepine to another antiepileptic drug, which showed no interaction with imatinib metabolism.

TABLE 4 Association[a] between gene activity score (GAS), corrected by drug–drug interaction, with imatinib, imatinib + nor-imatinib and nor-imatinib/imatinib plasma trough level in 33 patients undergoing treatment with imatinib 400 mg/die

	Imatinib		Imatinib + nor-imatinib	
	β	*P*	*β*	*P*
CYP3A4	*−152.3*	0.2230	*−167.6*	0.2472
CYP3A5	*468.5*	0.1974	*519.7*	0.2187
CYP2C8	*−213.8*	0.2977	*−208.0*	0.3878
CYP2D6	*−360.0*	0.0085	*−415.5*	0.0094
CYP2C9	*−206.4*	0.2794	*−259.8*	0.2437
CYP2C19	*74.0*	0.4671	*85.7*	0.4660

[a]Estimated on 161 blood samples using multilevel regression model, adjusting for gender and age at sampling.

4 | DISCUSSION

The well-documented interindividual variability in the clinical outcome of oral targeted therapies is partially correlated with individual changes in oral bioavailability among patients.[18] It was reported that only 45% of patients treated with oral targeted therapies are adequately exposed, 17% are overexposed with a risk of toxicity, and 38% are underexposed with risk of inefficacy.[19] The use of pharmacogenetics and the evaluation of its interplay with concomitant pharmacological treatments could help to customize dosing in patients affected by genetic polymorphisms impairing their ability to detoxify targeted drugs.[20]

In this study, we monitored the imatinib and (imatinib + nor-imatinib) plasma C_{trough} in a cohort of 33 GIST patients over several years to determine whether the GAS of imatinib-metabolizing CYPs and the concomitant intake of DDIs could affect the exposure to imatinib in GIST.

Our findings suggest that the GAS and the predicted metabolic phenotype of *CYP2D6* may help refine the prediction of imatinib plasma C_{trough} in GIST patients, sustaining a pivotal role for genetics in contributing to the interindividual variability of imatinib exposure at the steady state. Moreover, *CYP2D6* and *CYP2C8* were demonstrated to be associated with the ratio of metabolic conversion of imatinib to nor-imatinib.

As far as it is known, CYP3A4 is the major enzyme involved in the catabolism of imatinib, but it is mechanistically inhibited by imatinib itself in the course of treatment.[21] Therefore, it is reasonable to assume that at steady state a considerable portion of imatinib metabolism is dependent on other CYPs (e.g. CYP2D6 and CYP2C8) and could be affected by decreased/no function *CYP2D6* alleles.[22] Consistent with our findings, previous studies reported that patients carrying decreased/no function *CYP2D6* alleles (particularly *CYP2D6*4*) had slower oral clearance of imatinib than *CYP2D6* wild-type patients.[23] In our cohort, the *CYP2D6*4* allele had a frequency of 19.7%, which according to the literature is the most common no function allele in analysed patients.[24] However, a much more comprehensive characterization of *CYP2D6* allowed us to account for a more refined definition of no or decreased function alleles highlighting the effect of multiple other variants besides the *4 allele (e.g., *CYP2D6*5*). In our population, no patient was predicted to present increased function alleles (based on *CYP2D6* gene amplification). Therefore, wider association studies including more patients are needed to clarify the impact of CYP2D6 ultrarapid metabolizers on imatinib exposure.

We observed that patients who carry the *CYP2C8*3* increased function allele have significantly higher trough nor-imatinib/imatinib

metabolic ratio with respect to the *CYP2C8*1* carriers, while no impact of the *CYP2C8* genotype on the imatinib and (imatinib + nor-imatinib) C_{trough} was observed. Overall, the imatinib metabolic ratio showed a negligible intra-patient variability at the steady state, suggesting its poor susceptibility to external factors. These findings are consistent with previous data,[6] and strengthen the hypothesis based on in vitro studies that *CYP2C8*3* is an increased function allele that speeds up the conversion of imatinib into nor-imatinib.[25,26] Despite the disproportion between the two study cohorts, the 25% increase in metabolic ratio we observed in our study, mirrors the findings of Barratt et al, who reported an increase by 23% in 210 *CYP2C8*3* carrier chronic myelogenous leukaemia (CML) patients.[6] Most recently, *CYP2C8*3* was shown to significantly reduce the AUC of another metabolized drug such as cinitapride in healthy volunteers, further highlighting its implication in the clinical pharmacokinetics of CYP2C8 substrates.[27] Together with CYP3A4/5, CYP2C8 catalyses the N-demethylation of imatinib,[28] and was predicted to account for over the 60% of imatinib to nor-imatinib conversion at the steady state, when the activity of CYP3A4 is constrained by the mechanistic inhibition by imatinib.[26]

We also observed an effect of the *CYP2C9* metabolic phenotype on the nor-imatinib/imatinib metabolic ratio. This result appears controversial considering that patients with IM phenotype had a higher predicted metabolic ratio than normal metabolizers. In our patient series, seven of nine patients with a *CYP2C9* IM carried one or two decreased function *CYP2C9*2* alleles. All these seven patients simultaneously presented a *CYP2C8*3* increased function allele (Table S3) highlighting a situation of linkage disequilibrium between the two variants. The only two *CYP2C9* IM patients with a different genotype (i.e., *CYP2C9*1/*3*) presented a metabolic ratio in the lower range of values (Figure 1B). It was previously reported that *CYP2C9*2* and *CYP2C8*3* belong to the same long haplotype, and it has been shown that they often co-segregate in families.[29] That clinically relevant haplotype, recently shown to be inherited from Neanderthals,[30] could lead to paradoxical association results as in our study, where the observed effect appears to be driven by the increased function of the *CYP2C8*3* allele with a lower contribution of the *CYP2C9*2* decreased function allele.

On the other hand, our study highlighted that the broad consideration of potential DDGIs failed to add further value to the GAS in describing the phenotype, although low numbers in our study set could have disguised this effect. Still, a remarkable impact can be attributed to the concomitant intake of strong inducers (i.e., carbamazepine) in selected patients. Coadministration of imatinib and carbamazepine should be monitored closely as it could accelerate the imatinib clearance and expose patients at risk of therapeutic failure, and in fact the patient in our study appeared to be exposed to extremely low imatinib concentration.[31] The intake of carbamazepine also accounted for the highest nor-imatinib/imatinib metabolic ratio in the study cohort, and specifically in a *CYP2C8* wild-type patient, suggesting that the impact of a strong interacting drug can significantly overrule the effect of the underlying genetic background of the patient. The small number of patients who received strong inducers or strong enzyme inhibitors may have limited the possibility of showing a significant overall effect of these agents in the study set. The current ongoing debate on how to properly consider DDIs will likely provide better information on their actual effect on each individual's metabolizing status and their interaction with patient genotype.[9]

Consistently with previous data on GIST,[32,33] we observed that older patients have significantly higher imatinib and (imatinib + nor-imatinib) plasma C_{trough}. In fact, the progressive decline of organ function in elderly patients, together with the increased number of comorbidities contribute to reducing the metabolism of imatinib and to increasing its plasmatic exposure. Despite the occurrence of serious adverse reactions during imatinib being a rare event, our data sustain once again that elderly patients could possibly benefit from closer TDM in the course of imatinib treatment to limit the risk of dose-related side effects. On the other hand, the impact of gender on imatinib C_{trough} remains a matter of debate. Our data showed a non-significant trend of higher imatinib in female *vs.* male, which is consistent with previous studies reporting a non-significant increase of plasma imatinib levels in female patients.[34,35] Many reasons can account for gender discrepancies in drug dispositions, including hormonal status, BMI, body fat distribution and organ size,[36] making females overall more susceptible to drug-induced toxicity than males.

This study was the first to analyse the impact of DGIs and DDIs not only on the plasmatic levels of imatinib but also of nor-imatinib,[37] which shows in vivo potency similar to its parent drug but is generally neglected in pharmacogenetic studies. The joint analysis of imatinib and nor-imatinib allows us to precisely estimate the patients' exposure to the active compound, which might be underestimated when only imatinib is dosed. In fact, the interpatient variability in imatinib metabolic ratio makes it difficult to calculate the nor-imatinib fraction.

Despite these intriguing results, some limitations must be acknowledged in the present study. First, the size of the study population is modest, as GIST is a rare tumour entity, and validation of our findings in wider study cohorts remains warranted. However, the large number of available samples prospectively collected within the clinical trial allowed us to implement the statistical power of our model to account for not only inter- but also for intrapatient variability, a fundamental issue to consider when investigating the dynamic DDGI phenomenon. Moreover, despite the considerable number of comedications registered across the study cohort, a relatively small number of drugs capable of mediating DDGIs with imatinib was identified. However, a remarkable effect on the pharmacokinetics of imatinib was highlighted in the presence of the strong CYP inducer carbamazepine, suggesting that a careful appraisal of pharmacological interactions integrated with the TDM can help addressing complex phenomena responsible for therapeutic failure in imatinib-receiving GIST patients.

5 | CONCLUSIONS

In conclusion, we demonstrated that *CYP2D6* GAS is associated with both imatinib and (imatinib + nor-imatinib) C_{trough} in GIST patients, with a major role in imatinib conversion into nor-imatinib played by

CYP2D6 and CYP2C8. Our study provides preliminary evidence that the identification of genetic and environmental factors (i.e., DDIs) that may influence imatinib and (imatinib + nor-imatinib) disposition in GIST patients may help identifying the mechanisms responsible for the observed phenotype and support clinical decision making regarding imatinib dose adjustment. This finding could have important consequences considering the wide variability observed in the exposure to imatinib, with demonstrated clinical implications.[1,3] This study underlines once more how pharmacogenetics could be helpful when planning a treatment in a more personalized manner. Based on our results, a patient that is a carrier of a *CYP2D6* IM or PM could be at risk of treatment overexposure, whereas a patient carrying a *CYP2C8*3* allele could have a higher efficiency of conversion of imatinib to nor-imatinib possibly affecting the overall treatment efficacy. Many other factors contribute to imatinib treatment variability including age, gender and DDI, as demonstrated also by our data, and no guidelines for dose-managing based on phenotype/genotype are available to date. However, a baseline pharmacogenetic assessment could define which patients are at higher risk of treatment over- or under-exposure and could be better candidates for intensified pharmacological care including DDI revision and systematic TDM approaches to better optimize chronic dose. The ability to predict and tailor plasmatic exposure to imatinib in GIST patients could lead to safer and more effective treatment.[1,38]

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COMPETING INTEREST

The authors declare no conflicts of interest.

CONTRIBUTORS

C.D.F. and E.C. designed the study. C.D.F., E.C., S.G., J.P. and R.R. analysed the data. C.D.F., S.G., R.R., M.Z., M.B., B.P., E.D.M., R.B. and F.P. performed the research. L.F., M.G. and A.B. enrolled patients. C.D.F. and E.C. wrote the manuscript. G.T. supervised the research and contributed reagents.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request. Some data may not be made available because of privacy or ethical restrictions.

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SUPPORTING INFORMATION

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