Pharmacogenetics and drug-drug interactions affect imatinib pharmacokinetics in GIST patients. Results of an exploratory study

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ABSTRACT

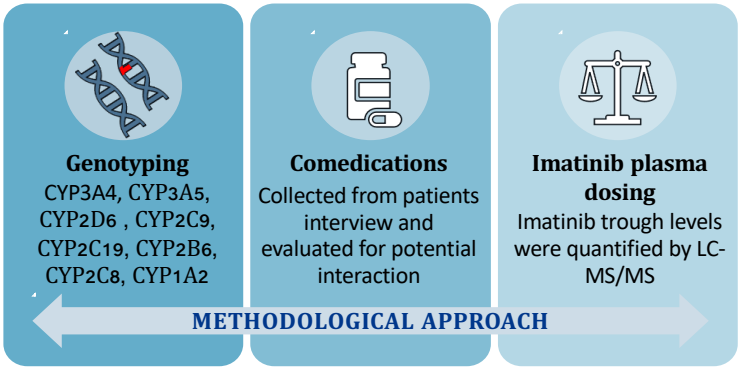
The huge inter individual variability of imatinib levels increases the risk of side effects in Gastrointestinal Stromal Tumor (GIST) patients. Here, the impact of pharmacogenetics variants affecting imatinib metabolizing enzymes and of potential drug-drug interactions (DDIs) on imatinib plasma levels was investigated. CYP2D6 activity score was found to affect imatinib exposure, while the joint assessment of genotype and DDIs showed to linearly correlate with imatinib levels. A specific association between CYP1A2 genotype, tobacco smoking and imatinib exposure has emerged.

BACKGROUND AND AIM

Imatinib is a tyrosine kinase inhibitor (TKI) used for the treatment of GIST. However, the huge pharmacokinetics variability in term of imatinib plasma concentrations in imatinib-receiving patients significantly increases the risk of **toxicity** or **lack of efficacy**[1]. Germline **genetic variants** affecting the activity of imatinib metabolizing enzymes could partially explain the variability in imatinib metabolism and significantly affect its plasma concentration[2]. Moreover, the concomitant administration of multiple medications (**polypharmacy**) could add further variability to the pharmacokinetics of imatinib, by inhibiting or enhancing its elimination rate.

The aim is to assess whether genetic variants in cytochromes (CYPs) involved in imatinib metabolism and the concomitant use of comedications could affect imatinib exposure in GIST patients.

MATERIALS AND METHODS

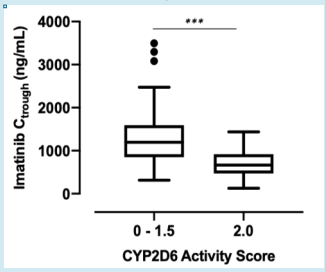


- **Genotyping** was performed on a panel of 36 genetic variants with documented functional impact on CYPs by means of allele-specific probes discrimination. A gene activity score (GAS) was assigned to each CYP to quantify their activity;
- The impact of **comedications** was assessed by interrogating 5 different biobanks: Drug-Bank, FDA, Lexicomp, Medscape and Flockhart Table. Interacting drugs were classified as inhibitors or inducers. A phenoconverted activity score (PGx_AS) was calculated to concomitantly consider the GAS and the impact of DDIs;
- Plasma was collected from consenting GIST patients who were on treatment with imatinib 400 mg/die. **Imatinib trough levels** were quantified by means of a validated LC-MS/MS method.

RESULTS

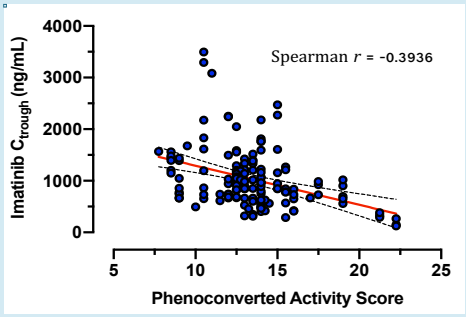
- 33 consenting GIST patients were prospectively enrolled from 2015 to 2020 and 124 sequential plasma samples were dynamically collected in course of imatinib treatment;
- Enrolled patients were co-administered with 0 to 9 drugs while on imatinib;
- 14 out of 33 (42.4%) patients were administered with at least one drug that could potentially affect the metabolism of imatinib.

CYP2D6 activity score affects imatinib exposure



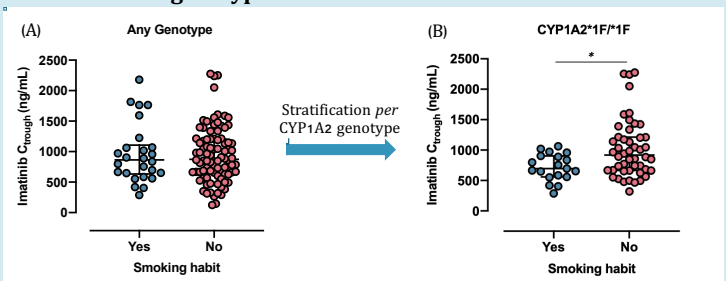
The genotype of *CYP2D6* was shown to significantly affect imatinib trough levels at the steady state. Specifically, patients who were poor or intermediate metabolizers (GAS = 0-1.5) for *CYP2D6* are over-exposed to imatinib with respect to the *CYP2D6* full metabolizers (GAS = 2.0) (Imatinib $C_{tr.}$: 1195 ng/mL *vs* 664 ng/mL, p < 0.0001). Other analyzed genes failed to correlate with imatinib trough levels.

The phenoconverted activity score (PGx-AS) inversely correlates with imatinib exposure



The phenoconverted activity score was used to put together the impact of genotype and of the DDIs to predict the metabolic phenotype of imatinib. Patients showing a higher PGx-AS due to either gain of function genetic variants or the co-ingestion of CYPs' inducers tends to have lower imatinib trough levels than patients with a lower PGx-AS, underlying a link between genetics, external factors (DDIs) and the resulting metabolic phenotype in the case of imatinib.

Tobacco smoke induces imatinib elimination in presence of CYP1A2*1F/*1F genotype



No difference in imatinib trough levels was observed between current smokers and non-smokers (A). However, the use of tobacco smoke was associated with lower imatinib exposure when patients were stratified according to their *CYP1A2* genotype. Smoker patients who were homozygous carriers of the *CYP1A1*1F* allele have significantly lower imatinib levels when comparted to non-smoker patients with the same genotype (Imatinib $C_{tro.}$: 696 ng/mL *vs* 917 ng/mL, p = 0.0149) (B). Indeed, tobacco smoke is a known inducer of CYP1A2, while the *1F genotype is the high-inducible allele of *CYP1A2*[3], thus explaining the effect of smoking only in presence of a specific genotype.

CONCLUSIONS

This exploratory study investigates for the first time the joint impact of pharmacogenetics and DDIs on imatinib pharmacokinetics, suggesting that both the genetics and the use of comedications might affect the metabolism of imatinib, thus possibly contributing to the development of side effects. These findings leave room for further investigation upon the interplay between genotype, DDIs and imatinib disposition in GIST patients.

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