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

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ABSTRACT

The huge interindividual 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 efficacy1. Germline genetic variants affecting the activity of imatinib metabolizing enzymes could partially explain the variability in imatinib metabolism and significantly affect its plasma concentration2. 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

CYP3A4, CYP3A5, CYP2D6, CYP2C9, CYP2C19, CYP2B6, CYP2C8, CYP1A2

Comedications

Collected from patients interview and evaluated for potential interaction

Imatinib plasma dosing

Imatinib trough levels were quantified by LC-MS/MS

METHODOLOGICAL APPROACH

• 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: DrugBank, Lexicomp, Medscape and Flochard 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.

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.