Sex Differences in Imatinib and Sunitinib Exposure: The Role of Pharmacogenetics and Therapeutic Drug Monitoring

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BACKGROUND

Imatinib (IMA) and Sunitinib (SUN) are oral tyrosine kinase inhibitors (TKIs) used in oncology. IMA treats gastrointestinal stromal tumors (GIST) and chronic myeloid leukemia (CML) at doses of 400-800 mg/day, while SUN is indicated for GIST and metastatic renal cell carcinoma (mRCC) at doses of 25, 37.5, or 50 mg/day. Both drugs show high interpatient variability in plasma exposure, influenced by pharmacogenetics and sex-related differences. IMA is metabolized by *CYP3A4/5* into norimatinib (NOR-IMA) and transported by *SLC22A1*, *SLCO1B3* (uptake), and *ABCB1/ABCG2* (efflux). SUN undergoes *CYP3A4/5* metabolism to N-desethyl sunitinib (N-DES) and is transported by ABCB1/ABCG2. Therapeutic targets: IMA C_{trough} >1100 ng/mL (efficacy) and >3000 ng/mL (toxicity); SUN C_{trough} (SUN+N-DES) 37.5-75 ng/mL (continuous) or 50-87.5 ng/mL (intermittent) for efficacy.

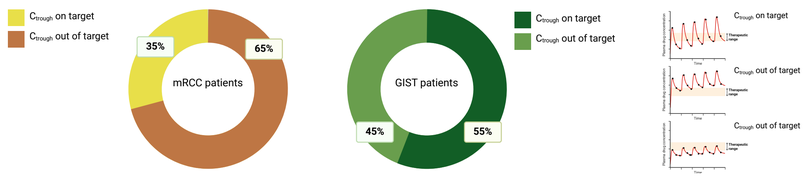


Figure 1. Percentage of mRCC and GIST patients who achieve adequate or non adequate C_{trough}

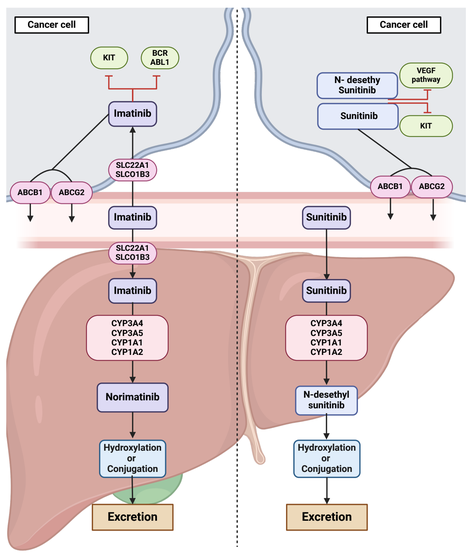
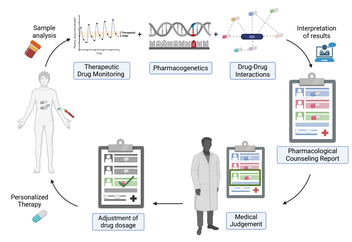


Figure 2. IMA and SUN metabolism and transport pathways

METHODS

Patients were enrolled in the CRO-2022-14 trial conducted at CRO Aviano. Samples were collected at minimum steady-state plasma concentration (C_{trough}), and exposure was determined by quantifying analytes C_{trough} using a validated LC-MS/MS method. Polymorphisms (SNPs) in IMA and SUN-related cytochromes and cell-transporters were analyzed. Oncologists received a pharmacological counselling based on interpreted data.



GENETIC POLYMORPHISMS ANALYZED:

- *CYP3A4* (rs35599367 - *22)
- *CYP3A5* (rs776746 - *3; rs10264272 - *6; rs41303343 - *7)
- *ABCB1* (rs1128503 - 1236C>T; rs104564 - 3435C>T; rs2032582 - 2677T>G>A)
- *ABCG2* (rs2231142 - 421C>A)
- *SLC22A1* (rs683369 - 480C>G; rs628031 - 1222G>A)
- *SLCO1B3* (rs4149117 - 334G>T)

Figure 3. Integrated pharmacological counseling process

RESULTS

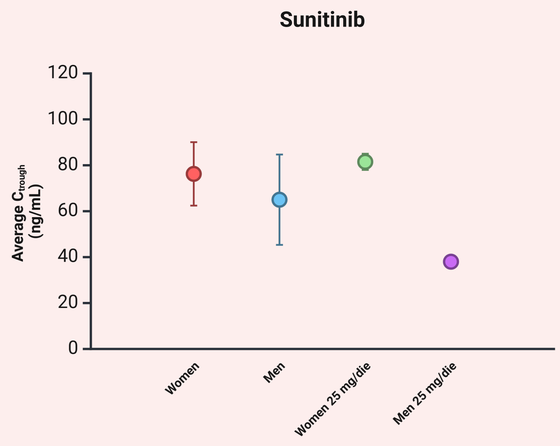


Figure 4. Average SUN C_{trough} (ng/mL) in women and men at any dosage, women and men at 25 mg/day.

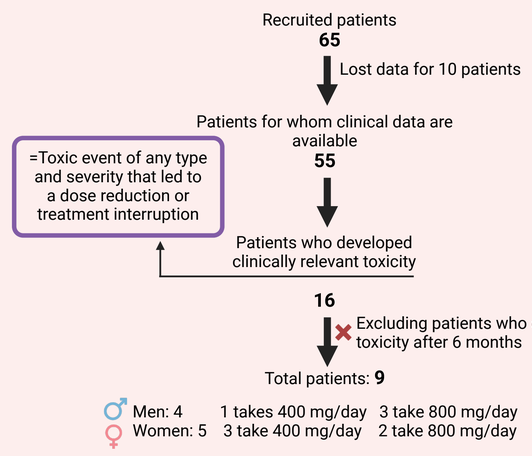


Figure 6. IMA patient selection for cumulative incidence of clinically relevant toxicity analysis

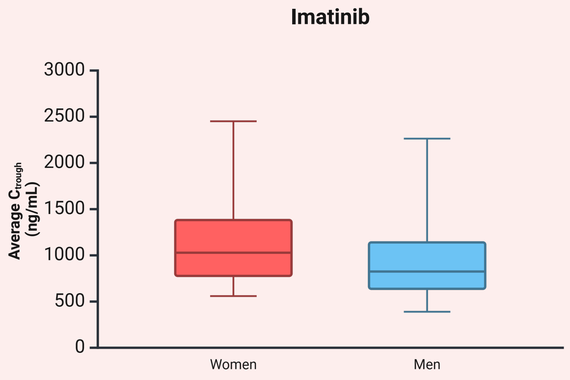


Figure 5. Average IMA C_{trough} (ng/mL) in women and men

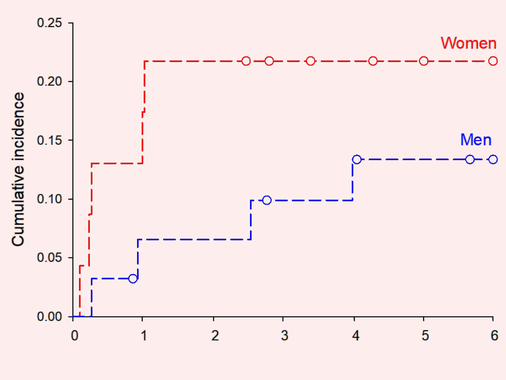


Figure 7. Cumulative incidence of clinically relevant toxicity in women (red) and men (blue) with GIST receiving IMA

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Gene	rsID	IMA mean C_{trough} (ng/mL) (StD)		p-value genotype	p-value sex
		Men	Women		
CYP3A4	**rs35599367**				
	CC	901 (467)	1169 (517)	---	0.026
	CT	-	1050 (254)		
CYP3A5	**rs776746**				
	GG	893 (421)	1158 (510)	---	0.025
	GA	955 (775)	1104 (252)		
ABCB1	**rs1128503**				
	CC	742 (317)	1210 (321)	---	0.050
	CT	979 (572)	1124 (632)		
	TT	827 (250)	1094 (611)		
ABCB1	**rs1045642**				
	CC	718 (273)	1385 (527)	---	0.021
	CT	969 (444)	1004 (277)		
	TT	922 (620)	1132 (593)		
ABCG2	**rs2231142**				
	CC	824 (460)	1193 (462)	0.048	0.008
	CA	935 (230)	1079 (560)		
	AA	1576 (749)	-		
SLCO1B3	**rs4149117**				
	GG	934 (532)	1106 (406)	---	0.021
	GT	804 (160)	1260 (665)		
SLC22A1	**rs683369**				
	CC	846 (436)	1125 (520)	0.035	0.010
	CG	857 (240)	1207 (452)		
	GG	2316 (-)	-		
SLC22A1	**rs628031**				
	GG	794 (363)	1184 (594)	0.004	0.008
	GA	807 (223)	1080 (398)		
	AA	2211 (148)	1820 (-)		

Table 1. Average C_{trough} of IMA according to SNPs by sex
The table shows IMA plasma concentrations (mean ± standard deviation) for different polymorphisms in key pharmacokinetic genes. To interpret the data, each SNP should be analyzed both horizontally, comparing men and women with the same genotype to assess sex-related differences, and vertically, comparing different genotypes within each sex to evaluate the impact of genetic variants on drug exposure. Red arrows serve as examples of these comparisons

For SUN, 16 patients were enrolled (12 men, 4 women), with only 2 women having GIST, while the rest had mRCC. At enrollment, patients had been on treatment for an average of 28 months, all with a reduced dosage due to toxicity. Women showed higher drug exposure, with an average C_{trough} of 76±14 ng/mL vs. 65±20 ng/mL in men. Among the four patients receiving 25 mg/day, women had significantly higher exposure (82±3 ng/mL) than men (38±1 ng/mL).
For IMA, only patients on 400 mg/day were considered (28 men, 23 women). Women had a higher mean C_{trough} (1153±489 ng/mL) than men (901±467 ng/mL). Clinically relevant toxicity within the first 6 months was observed in 9 patients, with women showing a higher cumulative incidence, suggesting that over time, women may be more susceptible to drug's side effects than men.
Stratification of IMA concentrations by SNPs confirmed that sex significantly impacts drug exposure, with women consistently showing higher C_{trough} regardless of genotype. Additionally, polymorphisms rs2231142 (*ABCG2*), rs683369 (*SLC22A1*), and rs628031 (*SLC22A1*) were associated with increased IMA concentrations in both sexes.

CONCLUSION

Women showed significantly higher plasma exposure to both imatinib and sunitinib compared to men, regardless of dosage and genotype. This increased exposure correlated with a higher incidence of clinically relevant toxicity in women, especially in the early months of treatment. Pharmacogenetic analysis confirmed that sex influences drug pharmacokinetics beyond genetic variability. These findings highlight the need for sex-specific therapeutic drug monitoring and personalized dosing strategies to optimize treatment efficacy while minimizing adverse effects.

DISCLOSURE AND FUNDINGS

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