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Clinical Pharmacokinetics of Imatinib: Evidence of Sex-Related Differences in Drug Exposure

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INTRODUCTION & AIM

Imatinib is a tyrosine kinase inhibitor (TKI) derived from 2-phenylaminopyrimidine, initially developed to target the platelet-derived growth factor receptor. It was subsequently shown to inhibit the BCR-ABL fusion protein and c-KIT. These kinases phosphorylate specific amino acids on substrate proteins, triggering signal transduction pathways involved in cell proliferation, differentiation, and survival. Constitutive activation of these pathways due to mutations or other mechanisms may lead to malignant transformation. By competitively inhibiting the ATP-binding site of ABL, imatinib prevents persistent tyrosine kinase activation and induces apoptosis in leukemic cells.

Imatinib plasma concentrations are known to correlate with clinical response, highlighting a strong pharmacokinetic–pharmacodynamic relationship. The aim of this study was to provide a comprehensive pharmacokinetic evaluation of imatinib exposure and to assess interindividual variability, with particular focus on differences related to sex and age, which are recognized as important determinants of drug pharmacokinetics.

METHOD

A monocentric cohort study was conducted at the Clinical Pharmacology Service “Franco Ghezzo” of San Luigi Gonzaga University Hospital (Orbassano, Turin, Italy). Adult and pediatric patients diagnosed with chronic myeloid leukemia and treated with imatinib for at least 6 months were included. Blood samples were collected at trough concentration (Ctrough) during routine therapeutic drug monitoring after informed consent was obtained.

Plasma imatinib concentrations were quantified using a validated high-performance liquid chromatography coupled with ultraviolet detection (HPLC–UV) method. Sample preparation included protein precipitation followed by chromatographic analysis using an Agilent 1100 HPLC system equipped with a C18 analytical column. Drug concentrations were measured under validated analytical conditions to ensure accuracy and reproducibility.

Demographic and clinical data, including age, sex, and treatment information, were collected. Statistical analyses were performed using IBM SPSS Statistics 25.0. Continuous variables were summarized as median and interquartile range (IQR). Differences between groups were assessed using the Mann–Whitney U test, with statistical significance set at $p < 0.05$.

RESULTS & DISCUSSION

The median age of the 60 patients undergoing imatinib therapy was 15 years (IQR 25–56.75 years), and 31 patients (51.7%) were paediatrics. The imatinib median plasma con-centration was 1.82 µg/mL (IQR 0.88–2.93 µg/mL), and CSF sampling was not performed on any of the included patients. A borderline correlation between imatinib plasma concentration and age was observed: $p = 0.073$, $r = -0.233$. A statistically significant difference in imatinib concentrations was observed between sexes, with higher concentrations in females compared to males ($p < 0.001$). After exclusion of paediatric patients, sex remained significantly associated with concentration levels, with adult females exhibiting significantly higher concentrations than adult males ($p < 0.001$). Among adult patients, 156 out of 325 (48.0%) had concentrations within the range of 1–3 mg/mL. This proportion was 45.0% in males (85/189) and 52.2% in females (71/136); however, this difference was not statistically significant.

Figure 1. Sex-related differences in imatinib plasma concentrations

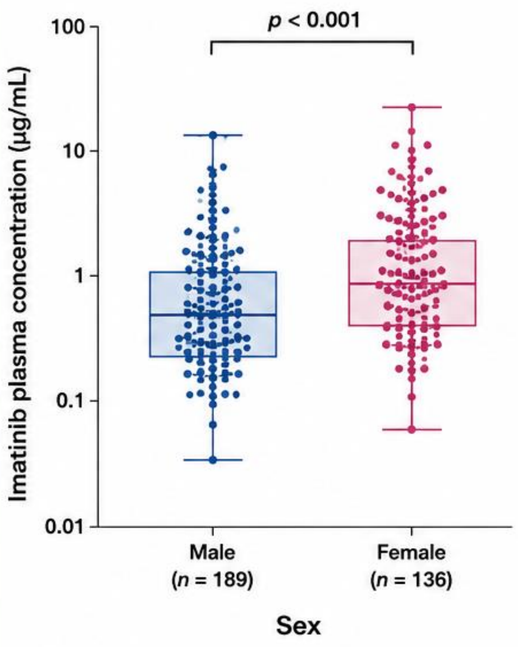

Figure 1. Sex-related differences in imatinib plasma concentrations. Distribution of trough imatinib plasma concentrations in male and female patients. Box plots represent the median and interquartile range (IQR), while whiskers indicate the minimum and maximum values. Female patients exhibited significantly higher plasma concentrations compared with male patients ($p < 0.001$, Mann–Whitney U test).

Figure 2. Influence of sex on imatinib exposure in adult patients

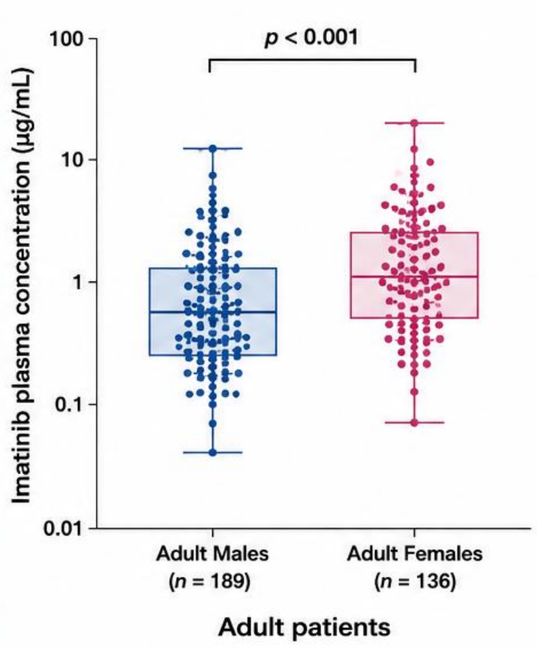

Figure 2. Influence of sex on imatinib exposure in adult patients. Comparison of trough imatinib plasma concentrations between adult male and adult female patients. Adult females showed significantly higher plasma concentrations than adult males ($p < 0.001$, Mann–Whitney U test), confirming sex as an important determinant of imatinib pharmacokinetics.

Figure 3. Proportion of patients within the therapeutic concentration range

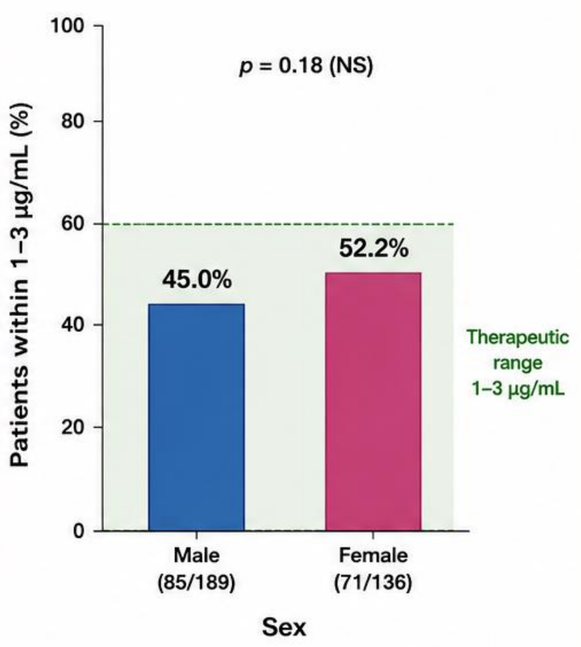

Figure 3. Proportion of patients within the therapeutic concentration range. Percentage of adult patients with imatinib plasma concentrations within the therapeutic range of 1–3 µg/mL. Although a higher proportion of female patients achieved target concentrations compared with males (52.2% vs. 45.0%), the difference was not statistically significant ($p = 0.18$, Fisher exact test).

CML, chronic myeloid leukemia; TKI, tyrosine kinase inhibitor; NS, not significant.

CONCLUSIONS

These findings confirm substantial interindividual variability in imatinib exposure and identify sex as a significant determinant of plasma concentration in adult patients. Consideration of sex- and age-related differences may support more individualized therapeutic drug monitoring strategies to optimize treatment efficacy and safety in oncology practice.

FUTURE WORK/ REFERENCES/ACKNOWLEDGMENT

Future research should investigate the biological mechanisms underlying sex-related differences in imatinib exposure and evaluate their impact on treatment efficacy and toxicity. Integrating therapeutic drug monitoring with pharmacogenetic and clinical data may improve personalized treatment strategies in oncology.