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Evaluating the Paradox: Lower Imatinib Trough Levels Associated with Higher Adverse Drug Reactions

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Introduction

Imatinib, a widely used tyrosine kinase inhibitor, has a therapeutic trough concentration (C0) reference range (RR) typically between 1000 and 3000 ng/mL. However, some patients have been found to have concentrations above 3000 ng/mL without exhibiting any signs of toxicity. This study aims to investigate the relationship between imatinib C0 and the occurrence of adverse drug reactions (ADRs), with a cut-off of 3000 ng/mL.

Methods

We conducted a retrospective comparative study that included all imatinib concentration measurements referred to the Clinical Pharmacology Department of the Tunisian National Center of Pharmacovigilance between 2009 and 2024. Measurements were divided into two groups:

Group A (C0<3000 ng/mL)

Group B (C0 > 3000 ng/mL)

Imatinib plasma concentrations were quantified using a validated in-house High-Performance Liquid Chromatography (HPLC) method.

Results

A total of 236 imatinib C0 from 177 patients were analyzed. The sex-ratio (M/F) was 1.8, with a mean age of 49.4 ±17.1 years and a median weight of 72.8 kg [18-280kg]. The mean imatinib C0 was 2309.3 ±2061.2 ng/mL, and the mean daily dose was 455.9 ±204.5 mg. Group B included 47 C0 measurements above 3000 ng/mL from 36 patients, with an average C0 of 5315 ± 2274.1 ng/mL.

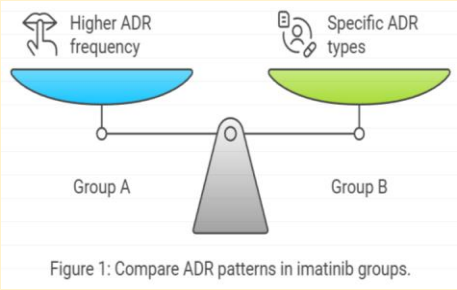

Figure 1: Compare ADR patterns in imatinib groups.

Although the frequency of ADRs was higher in Group A (41%) compared to Group B (34%), this difference was not statistically significant (p=0.4).

In Group A, the most frequently reported ADRs were gastrointestinal (17%) and cutaneous reactions (15%). In contrast, Group B experienced mainly hematologic toxicity (32%) and gastrointestinal reactions (23%). **(figure1)**

Discussion

The mean imatinib C0 was found to be 2309.3ng/mL, with a notable subset of patients exhibiting levels>3000 ng/mL without an increase in ADR frequency. This suggests that individual patient factors, including metabolic differences and concomitant medications, may play a critical role in how imatinib is tolerated. The lack of a statistically significant difference in ADR rates between the tow groups indicates that the RR may be broader than previously thought [1].

The study's results indicate distinct profiles of ADRs associated with different imatinib concentration ranges. In Group A, gastrointestinal issues and cutaneous reactions were predominant, while hematologic toxicities were more common in Group B. This divergence highlights the complexity of ADRs associated with imatinib therapy, suggesting that higher plasma concentrations may predispose patients to specific types of toxicity, particularly hematologic effects such as thrombocytopenia.

The predominance of gastrointestinal and cutaneous reactions at lower concentrations may reflect a different mechanism of action or sensitivity at those levels [2].

Conclusion

In conclusion, this study highlights that higher plasma concentrations of imatinib do not necessarily correlate with increased toxicity but rather reflect a complex interplay of pharmacokinetics and individual patient factors. The distinct ADR profiles associated with varying concentration ranges emphasize the need for personalized treatment approaches to enhance safety and therapeutic efficacy in CML management.

References

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