Original Article

Pharmacogenomic Insights Into The Response To Imatinib In Chronic Myeloid Leukaemia: The Role Of CYP3A4 Polymorphisms

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Abstract

Objective: To investigate the effect of CYP3A4 polymorphisms rs2740574 and rs2242480 on the response to Imatinib Mesylate in treatment-naïve patients with chronic myeloid leukaemia (CML).

Methods: It was a prospective, non-interventional observational genetic association study involving 106 treatment-naive CML patients genotyped for rs2740574 and rs2242480. According to the Helsinki Declaration, the study was conducted in compliance with current good clinical practices and was approved by the Ethical Review Committee. Blood samples and clinical data were collected in the pathology department between March 2018 and March 2020. Informed consent was obtained from all participants. Treatment response was evaluated at 3 months based on complete hematologic response (CHR) and plasma Imatinib levels.

Results: Patients with wild-type homozygous genotypes for both polymorphisms exhibited higher CHR rates (75% vs. 50% and 30% for rs2740574; 80% vs. 55% and 35% for rs2242480).

Conclusions: CYP3A4 polymorphisms rs2740574 and rs2242480 predict Imatinib response. Early detection of non-responders based on polymorphism analysis before treatment initiation allows timely initiation of second-generation Tyrosine Kinase Inhibitors (e.g., dasatinib, nilotinib), thereby avoiding ineffective Imatinib therapy and facilitating earlier achievement of treatment-free remission.

Keywords: Tyrosine Kinase Inhibitors, Leukaemia, Imatinib Mesylate, Cytochrome P-450 Cyp3A4, Pharmacogenetics.

Introduction

Chronic myeloid leukaemia (CML) is a malignancy that originates from hematopoietic stem cells, typically characterised by the presence of the Philadelphia chromosome (Ph) and the BCR-ABL1 fusion gene.[1] The advent of tyrosine kinase inhibitors (TKIs) targeting BCR::ABL1, with imatinib as the prototype, has transformed the therapeutic landscape of CML. This breakthrough has led to significant enhancements in patient survival and quality of life, with 10-year survival rates now approaching 90%, often resulting in long-term disease remission. Recently, clinical efforts have shifted toward optimising patient well-being and reducing the risks of chronic toxicities. A major area of interest is achieving "treatment-free remission" (TFR), where TKIs can be discontinued safely without disease relapse.[2] The development of second- and third-generation TKIs—such as dasatinib, nilotinib, bosutinib, and ponatinib—has further expanded treatment options, showing potent and rapid molecular responses. However, the durability of responses and long-term safety profiles of these newer agents remain under investigation. Additionally, second-generation TKIs may lead to serious, sometimes life-threatening, adverse events, and their high cost limits widespread use. By contrast, imatinib remains the globally preferred first-line treatment due to its well-established efficacy, favourable safety profile, and cost-effectiveness, particularly for older adults.[3]

Treatment decisions are guided by monitoring BCR::ABL1 transcript levels using the International Scale (IS) at key time points—3, 6, and 12 months—with additional assessments required if response patterns are unclear or if dose modifications are necessary due to toxicity. Achieving a major molecular response (MMR), defined as BCR::ABL1 $\leq 0.1\%$, is associated with near-complete protection against disease progression and a CML-specific survival rate close to 100%.[4] Nonetheless, about 20–30% of patients may need to discontinue imatinib due to inadequate cytogenetic or molecular response.[5]

Resistance to imatinib can arise through various mechanisms, such as overexpression of BCR::ABL1, additional chromosomal abnormalities, or mutations within the BCR::ABL1 kinase domain. Moreover, limited intracellular availability of imatinib contributes to suboptimal therapeutic outcomes. Imatinib's pharmacokinetics are influenced by its interaction with membrane transporters: it is exported by ATP-binding cassette (ABC) transporters like ABCB1 and ABCG2, and imported via the human organic cation transporter 1 (OCT1; encoded by *SLC22A1*).[6] Additionally, it undergoes hepatic metabolism primarily through cytochrome P450 enzymes, particularly CYP3A4 and CYP3A5. These genetic and metabolic pathways—including *ABCB1*, *ABCG2*, *SLC22A1*, *CYP3A4*, and *CYP3A5*—are believed to affect both systemic and intracellular drug concentrations.[7] CYP3A4, a major enzyme involved in the metabolism of a wide range of drugs, exhibits significant polymorphic variation in the human population. In the context of CML treatment, understanding the relationship between CYP3A4 polymorphism and Imatinib response is crucial for optimising therapeutic outcomes.

The genetic variations in CYP3A4, particularly involving rs2740574 and rs2242480, have been a subject of intense study, with implications for the efficacy and safety of Imatinib therapy in CML patients. Notably, the presence of specific alleles has been linked to differences in drug metabolism and treatment outcomes.[8] Of

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particular interest is the observation that individuals with the wild-type homozygous genotype for these polymorphisms tend to exhibit better responses to Imatinib compared to those with rare homozygous or heterozygous genotypes.

The polymorphic nature of CYP3A4 and its implications for Imatinib therapy in CML underscore the importance of genetic variability in drug response. The influence of rs2740574 and rs2242480 on Imatinib metabolism and treatment outcomes emphasises the need for personalised approaches to patient care. By integrating genetic information into treatment decision-making, medical researchers and doctors can improve the efficacy and safety of Imatinib therapy, ultimately enhancing the management of CML and advancing the field of precision medicine. Furthermore, haplotype analysis has provided valuable insights into the combined effects of multiple genetic variants within the CYP3A4 gene. While individual polymorphisms may exert modest effects on drug metabolism and response, examining their collective influence through haplotype analysis has revealed non-significant inheritance patterns when considering two specific variants together. This finding highlights the complexity of genetic interactions and emphasises the need for comprehensive assessments of genetic polymorphisms to fully appreciate their impact on drug therapy.

In this study, we aimed to evaluate the influence of genetic variants on imatinib pharmacokinetics and treatment outcomes. We explored the impact of the CYP3A4 rs2740574 and rs2242480 polymorphisms on imatinib metabolism and clinical response in CML patients, with particular focus on the genotype differences between wild homozygous, heterozygous, and rare homozygous individuals, and to assess the significance of the combined inheritance of these loci.

Materials And Methods

This prospective, observational, non-interventional genetic association study was conducted at the Department of Pharmacology and Therapeutics. The study was approved by the (Approval No. Ref#Riphah/IIMC/ERC/19/0265) on July 25, 2019. The research adhered to international ethical standards, including the Declaration of Helsinki and the International Conference on Harmonisation – Good Clinical Practice (ICH-GCP) guidelines. Participants provided informed written consent, were assured of data confidentiality, and were informed of their right to withdraw at any point without any financial repercussions. As an observational study, no direct drug interventions were administered, ensuring minimal risk to participants.

Patients newly diagnosed with chronic myeloid leukaemia (CML) were recruited from the CML clinic at Holy Family Hospital. Inclusion criteria encompassed treatment-naïve individuals aged 18–70 years, positive for the Philadelphia chromosome (Ph+), receiving a daily dose of 400 mg imatinib, without comorbidities, demonstrating good treatment compliance, and no concomitant medications affecting CYP3A4 or CYP3A5 enzymes. A non-probability consecutive sampling technique was employed. Initially, 120 patients were considered; however, after excluding those with non-compliance or comorbidities, the final sample comprised 106 participants. Using G*Power (v.3.1), our sample (n = 106) provides 90% power at $\alpha = 0.05$ to detect medium effect sizes. Thus, the study is adequately powered for moderate-to-large associations but not for the small effects and this is also mentioned in the limitations of the study.

Treatment response was monitored following the European LeukemiaNet 2020 guidelines. Patients were monitored for hematologic response at 3 months. Patients achieving complete haematological response after three months of imatinib therapy were classified as responders and continued on the same regimen for an additional three months to confirm sustained response. Non-responders, identified by the absence of a complete haematological response after three months with a positive Philadelphia chromosome.

Genomic DNA was extracted from blood samples using the Thermo Scientific GeneJET Whole Blood Genomic DNA Purification Mini Kit, following the manufacturer's instructions. This method has been previously validated for yielding high-quality DNA.[10] The CYP3A4 rs2242480 polymorphism was analysed using the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) technique, as described in prior studies. Allele-specific primers were designed for the rs2740574 (CYP3A4).

Peripheral blood samples were collected from patients approximately 24 ± 2 hours after their last imatinib dose. To ensure the achievement of steady state concentration, patients maintained a stable daily dosing regimen for at least one month before sampling. Blood samples were processed promptly by centrifugation at 4°C to separate plasma and serum, which were then stored at −80°C until analysis. Imatinib mesylate, provided by Novartis Pharma (Basel, Switzerland), served as the internal standard in the assay system, which was approved by Novartis Pharma.

Statistical analyses were performed using IBM SPSS Statistics versions 22.0 and 23. Descriptive statistics summarised group data as mean ± standard error of the mean (SEM). Categorical variables were compared using the chi-square (χ^2) test. To assess adherence to Hardy-Weinberg equilibrium, a χ^2 test was applied to genotype frequencies, evaluating deviations from expected distributions. Binary logistic regression analysed the association between genotypes and treatment response, estimating odds ratios and confidence intervals. Analysis of variance (ANOVA) compared imatinib plasma levels across different genotypic groups. A p-value less than 0.05 was considered statistically significant.

Results

Our findings demonstrate a significant association between polymorphisms in the CYP3A4 gene—specifically rs2740574 and rs2242480—and therapeutic response to Imatinib, as well as variations in plasma drug levels, highlighting the potential pharmacogenetic implications in chronic myeloid leukaemia (CML) treatment.

Genotype Distribution and Therapeutic Response

For both SNPs, the CC genotype was the most prevalent (rs2740574: 58%; rs2242480: 54%). Therapeutic response was significantly higher among CC carriers compared to CT and TT genotypes, with 71% (rs2740574) and 66% (rs2242480) of CC individuals responding positively to imatinib. In contrast, TT carriers exhibited the lowest response rates (rs2740574: 3%; rs2242480: 7%), with highly significant p-values ($p < 0.001$ and $p = 0.012$, respectively) as shown in Figure 1.

Logistic Regression Analysis

Binary logistic regression further supported these associations. For rs2740574, individuals with the TT genotype had a significantly lower odds of therapeutic response compared to CC (OR = 0.11; 95% CI: 0.021–0.55; $p = 0.007$). A similar trend was observed for rs2242480 (OR = 0.0205; 95% CI: 0.056–0.755; $p = 0.017$). The CT genotype also showed reduced response odds, reaching significance for rs2242480 ($p = 0.024$). These data underscore a gene-dose effect, wherein increasing T allele presence corresponds to diminished therapeutic response.

Findings of Plasma Imatinib concentration are shown in Figure 2 with means of values in all patients and among responders across different genotypes.

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Plasma Imatinib Levels in All Patients:
For patients with the CC genotype, the mean plasma imatinib level was 1123 ng/ml for the rs2740574 polymorphism ($p = 0.17$) and 1244 ng/ml for the rs2242480 polymorphism, which was statistically significant ($p = 0.000$**).
Among those with the CT genotype, mean plasma levels were 1156 ng/ml for rs2740574 and 988 ng/ml for rs2242480.
For patients with the TT genotype, the mean levels were 939 ng/ml for rs2740574 and 893 ng/ml for rs2242480.
Plasma Imatinib Levels in Responders:
In treatment responders with the CC genotype, the mean imatinib plasma level was 1189 ng/ml for rs2740574 ($p = 0.14$) and 1360 ng/ml for rs2242480 ($p = 0.01$*).
Responders carrying the CT genotype had mean levels of 1393 ng/ml for rs2740574 and 1035 ng/ml for rs2242480.

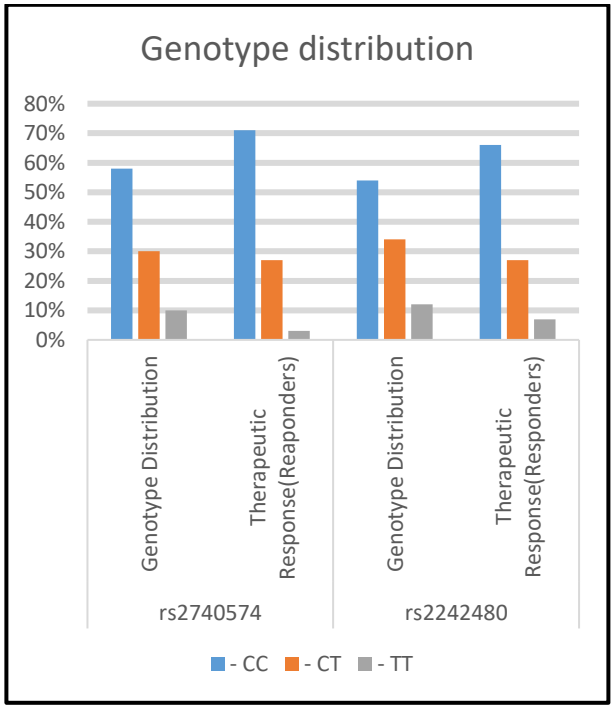

Figure 1: Genotype Distribution and Therapeutic Response in rs2740574 and rs2242480

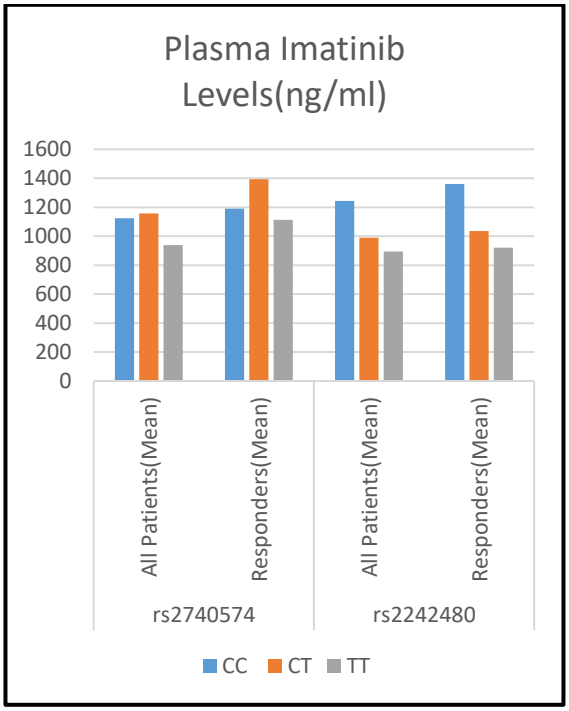

Figure 2: Mean Imatinib levels in responders and all patients in genotypes

Genetic Model Analysis
Significant associations were observed under codominant, dominant, and additive models for both SNPs (e.g., rs2740574 additive model: **p = 0.002**). The recessive model reached significance only for rs2740574 ($p = 0.018$), suggesting that homozygosity for the T allele is particularly detrimental in this context. (Table 1)

Table 1: Comparison of genetic models in rs2740574 & rs2242480

Model / Comparison	rs2740574	rs2242480
CT vs. CC	OR = 0.43 (95% CI: 0.184–1.024), $p = 0.057$	OR = 0.369 (95% CI: 0.156–0.875), $p = 0.024$
TT vs. CC	OR = 0.11 (95% CI: 0.021–0.55), $p = 0.007$**	OR = 0.0205 (95% CI: 0.056–0.755), $p = 0.017$*
Genetic Models	Codominant: $p = 0.010$* Dominant: $p = 0.006$** Recessive: $p = 0.018$*	Codominant: $p = 0.012$* Dominant: $p = 0.008$** Recessive: $p = 0.064$
Additive Model	p = 0.002**	p = 0.002**

Gender and Age Interactions
Gender-based interaction was significant for rs2242480 in females (p = 0.000), but not in males ($p = 0.588$), indicating a possible sex-specific genetic modulation of CYP3A5 activity, potentially mediated by hormonal influences. Age interactions, however, were not significant across both SNPs.

Discussion

Our findings provide compelling evidence for the pharmacogenetic role of CYP3A4 polymorphisms (rs2740574 and rs2242480) in predicting therapeutic response and plasma levels of Imatinib in patients with chronic myeloid leukaemia (CML). Both single-nucleotide polymorphisms

(SNPs) displayed significant associations with treatment efficacy, with CC genotypes exhibiting higher response rates and elevated plasma drug concentrations compared to TT genotypes, suggesting a gene-dose effect wherein increased T allele presence corresponds to diminished drug efficacy.[11]

CYP3A4 is a key enzyme involved in the metabolism of Imatinib, and inter-individual variability in drug response may be partially explained by polymorphisms in this gene. The rs2740574 polymorphism, located in the promoter region, has been associated with altered transcriptional activity and enzyme expression.[12] Studies support our findings that the CC genotype is linked to higher plasma Imatinib levels and better therapeutic outcomes.[13] For example, recent analyses in CML patients from diverse backgrounds confirm that rs2740574 wild-type carriers experience superior responses to therapy compared to variant allele carriers.[14]

Similarly, for rs2242480, a synonymous variant in exon 10, significant differences in Imatinib plasma levels among genotypes have been previously documented.[15] Qiu et al. observed that carriers of the A allele exhibited markedly lower trough concentrations (2.27 vs. 4.12 ng/mL/mg; $p = 0.017$) and reduced efficacy, highlighting this SNP's impact on drug metabolism.[16] Additionally, a 2020 study in Chinese GIST patients found that rs2242480 GG carriers had higher dose-adjusted trough levels than T-carriers ($p<0.05$).[17]

Conversely, rs2740574 (*1B) has more equivocal evidence in CML. While our data demonstrate strong associations with therapeutic response, a 2022 population pharmacokinetic study in 49 CML patients found no significant impact of CYP3A4 SNPs—including rs2740574—on Imatinib clearance.[18] This suggests that inter-study differences, possibly in ethnic background or sample size, may modulate detectable effects of this SNP.

The significance of codominant, dominant, and additive models for both SNPs supports a dose-dependent effect of the T allele in reducing drug responsiveness. Importantly, the recessive model achieved significance only for rs2740574, reinforcing the idea that homozygosity for the T allele (TT) may be especially detrimental.[19] These results are consistent with the literature showing T allele carriage (especially in homozygous form) to be predictive of poorer therapeutic response.

However, some studies present contrasting evidence. A 2023 pharmacogenetic study found no significant association between the rs2740574 polymorphism and Imatinib plasma levels or response in a Korean cohort, suggesting that the impact of CYP3A4 polymorphisms may be population-specific and influenced by genetic background, environmental factors, and co-medications.[20]

The observed trend of higher plasma Imatinib concentrations among responders and lower levels in non-responders, especially those carrying the TT genotype, supports the premise that genotype-dependent metabolism significantly influences drug exposure. Notably, **rs2242480** showed a statistically significant difference in plasma levels even among all patients, highlighting its stronger pharmacokinetic relevance. This aligns with previous GIST studies where genotype significantly influenced levels.

Yet, it is important to note that other factors, such as drug transporters (e.g., ABCB1, OCT1), co-medications, adherence, and hepatic function, also play critical roles in determining drug levels and response.[21] Thus, while CYP3A4 polymorphisms contribute to variability, they represent only a piece of a complex pharmacogenomic puzzle.

Contrasting our findings, the 2022 PK study in CML patients concluded no pharmacogenetic relevance of CYP3A4 polymorphisms post–dosing[8], highlighting the need for cautious interpretation. Ethnicity may contribute; the strong associations for rs2242480 observed in Han Chinese and GIST populations may not fully replicate in mixed CML cohorts. Furthermore, in vitro work on CYP3A4 variants confirms that enzyme activity can vary significantly across alleles and substrates.[22]

The significant association of rs2242480 with therapeutic response in females but not in males suggests potential sex-specific modulation of CYP3A4 expression, possibly mediated by estrogen and other hormonal influences. This aligns with reports that CYP3A4 expression is higher in females, potentially affecting drug metabolism rates.[23] However, this observation requires further investigation, as few studies have specifically examined sex–gene interactions in the context of Imatinib response.

Pharmacogenetic testing for rs2242480—and possibly rs2740574—could enable more personalised Imatinib therapy. CC carriers may tolerate standard dosing, while T-allele carriers (especially TT homozygotes) might benefit from higher starting doses or therapeutic drug monitoring. These adjustments could optimise plasma exposure and improve response rates, though balanced against toxicity risks.

Strengths include a focus on genotype–plasma level–response triad and thorough analysis via multiple genetic models. Yet limitations exist: smaller sample sizes may reduce detection of subtle effects, particularly sex-interactions; confounding variables like diet, co-medication, and comorbidities were not fully accounted for; and findings may not generalise across different ethnicities. Plasma Imatinib levels are influenced by multiple pharmacokinetic and pharmacodynamic factors beyond CYP3A4 genotype.

Population stratification could affect allele frequencies and associations.

Conclusions

In summary, our study supports a pharmacogenetic role for *CYP3A4 rs2242480*—and to a lesser extent *rs2740574*—in influencing Imatinib exposure and clinical response in CML patients. While supporting evidence is emerging, particularly for rs2242480, conflicting results highlight the complexity of translating pharmacogenetics into clinical practice. Future work involving larger, ethnically diverse cohorts, comprehensive pharmacokinetic modelling, and functional enzyme assays is essential to determine the predictive utility of these variants and guide tailored dosing strategies.

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