Summary

Introduction

Patients with chronic myeloid leukemia (CML) are usually treated with imatinib 400 mg/day. Despite excellent therapeutic response to imatinib, 20 - 30 % patients are resistant to this treatment. Several molecular mechanisms leading to imatinib resistance have been proposed (amplification and overexpression of the BCR/ABL1 gene, point mutations). It has been suggested that one of the reasons for the varied response to imatinib may be due to inter-individual differences in imatinib metabolism.

Objective

The primary goal was to find new biological parameters which could clarify the cases of unexplained imatinib failure. In our study we analyzed the influence of polymorphism in seven genes linked to the pharmakokinetics of imatinib: CYP3A5*3 (rs 776746), CYP3A4*1 (rs 2740574), CYP2C9*3 (rs 1057910), SLCO1 (rs 683369), ABCB1 (rs1045642, rs 1128503), ABCG2 (rs 2231142) and ABCC2 (rs 717620). We evaluated the association of these polymorphisms in optimal response and plasma levels of imatinib. The secondary objective was to evaluate whether the standard dose of imatinib 400 mg/daily leads to achieving optimal therapeutic response and whether this dose induces a sufficient plasma levels of imatinib.

Methods and results

We analyzed 112 patients with CML. Our cohort included 53 men (47 %) and 59 women (53 %) with a median age at diagnosis of 56 years (range 19-84 years). Median follow-up was 92 months (M) (range 29 to 230 M). Determination of plasma levels of imatinib was performed by high performance liquid chromatography analysis validated with a detection limit of 10 ng / ml. Peripheral blood samples of patients were performed 24 +- 2 hours before the next dose of imatinib. Detection of single nucleotide polymorphisms was performed using allele discriminating real-time PCR using dual labeled TaqMan probes hydrolyzation. Commercial genotyping assay and commercial master mix which contained the necessary components for PCR reaction was used for detection. Evaluation of treatment response in patients was made according to ELN (European Leukemia Net) guidelines from 2013.

Conclusions

We found no impact of any of the eight analyzed polymorphisms in genes CYP3A5*3, CYP3A4*1, CYP2C9*3, SLC22A1, ABCB1, ABCG2 and ABCC2 on the plasma levels of imatinib. Regarding the secondary objective of our study, a trend towards higher CCyR (complete cytogenetic response) rate at 6 months in patients with polymorphism CYP3A5*3 ($p = 0.06$) was observed, in addition genotype CC with other genotypes (TC/TT) showed a higher rate of optimal response ($p = 0.06$). CYP3A5*3 polymorphism was associated with higher CCyR rate at 12 months of treatment ($p = 0.01$). ABCG2 polymorphism had mild impact on achieving MMR (major molecular response) at 12 months treatment, including benefits of GG genotype compared with TG/TT ($p = 0.06$). Polymorphisms in genes CYP2C9*3, CYP3A4*1, SLC22A1, ABCB1 have shown no impact on the optimal therapeutic response.

Keywords: chronic myeloid leukemia, imatinib, treatment, polymorphism