The role of pharmacometrics in unraveling the effect of hOCT1 polymorphism c.480C>G on the pharmacokinetics of imatinib in patients affected by chronic myeloid leukemia

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Imatinib (Gleevec®, STI471) is the first tyrosine-kinase inhibitor for the treatment of chronic myeloid leukemia (CML), but its therapeutic benefit may be dependent on several pharmacokinetic and pharmacogenetic factors, as well as on patient's compliance. In fact, some studies have suggested that minimum plasma levels (Cmin) of imatinib higher than 1 mg/L could be associated with better molecular and cytogenetic response, despite some concerns are still present (Picard et al, 2007; Ishikawa et al, 2010; Faber et al, 2012). Furthermore, single nucleotide polymorphisms (SNPs) in several genes encoding for transmembrane transporters (among which the human organic cation transporter 1, hOCT1) have been identified as predictor of response (Maffioli et al, 2011). Interestingly, hOCT1 is also expressed in liver and kidneys, hence it could play a role in the elimination of drugs (Jonker et al, 2001, 2003). Therefore, the TIKlet study was aimed at evaluating a possible correlation between the pharmacogenetics of hOCT1 and imatinib pharmacokinetics in CML patients. The study was approved by the local Ethics Committee of the Azienda Ospedaliero Universitaria Pisana.
The effect of the hOCT1 c.480C>G single nucleotide polymorphism (SNP) on the pharmacokinetics of imatinib was investigated in 33 men and 27 women (median age and range, 56 and 27-79 years, respectively) affected by CML and treated with the drug for at least 2 weeks. Patients were consecutively enrolled, providing a signed informed consent to study participation. Further inclusion criteria were a proved compliance and the attendance to follow-up visits. The administration of other drugs or herbal products and smoking habit were allowed, but they had to be known. At first visit, a blood sample was obtained from a peripheral vein to measure plasma concentrations of imatinib (as well as at every follow up visit within the next 6 months after enrolment) and to perform pharmacogenetic analyses. Of note, every blood sample was obtained regardless the time elapsed from drug intake. Plasma concentrations of imatinib were measured by using a commercially-available kit (Chromsystems, Munich, Germany) on Breeze and Alliance instruments (Waters, Milford, CT). Patient's genotype with respect to the c.480C>G polymorphism was obtained by a real-time PCR method using an Applied Biosystem kit (Life Sciences, Milan, Italy) on an ABI Prism 7900HT Sequence Detection System (Life Sciences). In order to obtain individual pharmacokinetic parameters, a nonlinear mixed-effect modeling analysis was adopted using the NONMEM software, version 7.1. Results showed that plasma concentrations of alpha1 acid glycoprotein have a significant effect on both apparent drug clearance (CL/F) and apparent volume of distribution (V/F), whose mean values accounted for 11.6±4.0 L/h (median, 10.7 L/h) and 331.3±69.0 L (median, 367.2 L), respectively. More interestingly, the hOCT1 genotype had a significant effect on apparent drug clearance (CL/F) being responsible for a ≈10% decrease in interindividual variability of CL/F. In particular, 25 patients carrying at least one polymorphic G allele had a significant lower CL/F value with respect to the 35 individuals homozygotes for the C allele (9.5±1.5 *vs*. 12.2±2.3 L/h, respectively; $p<0.001$). In agreement with these results, CC individuals were characterized by significant lower Cmin,ss values with respect to the other patients (0.910±0.325 *vs*. 1.293±0.321 mg/L, respectively; $p<0.001$). In conclusion, the c.480C>G SNP may significantly influence imatinib pharmacokinetics, paving the way for further analyses in larger groups of patients.

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