Pharmacogenetic determinants of imatinib, dasatinib and nilotinib pharmacokinetics in chronic myeloid leukaemia patients.

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Imatinib is the gold standard for the treatment of chronic myeloid leukaemia (CML) [1]. Several studies revealed correlation between imatinib trough plasma levels and clinical response, suggesting that measurement of plasma levels can be an useful tool for optimising therapy [2]. It's known that antitumor imatinib efficacy is observed with plasma concentrations ≥1mg/l [2], although differences in concentrations are reached in some patients receiving the same drug dose. Furthermore up to 40% of CML patients show resistance or intolerance to imatinib, leading, as a consequence, a switching therapy to more potent tyrosine kinase inhibitors (TKIs) such as nilotinib and dasatinib. New TKIs, in fact, showed activities both in first and in second line treatment, overcoming imatinib as front-line treatment for CML, even if literature is still limited about the correlation between nilotinib and dasatinib plasma levels and clinical responses. Measurement of intracellular level of imatinib, furthermore, could become an important strategy to predict the efficacy of treatment in CML patients.

Primary aim of our study was to assess the impact of pharmacogenetic (PG) variability on plasmatic pharmacokinetics (PK) of imatinib, nilotinib and dasatinib. Drugs plasma trough levels have been determined by High Pressure Liquid Chromatography coupled with UV detection (HPLC-UV) validated method [3]. Candidate genes for PG analysis included ABCB1 and SLCO1B1, encoding for transporter proteins. After DNA extraction from blood red cells, Real Time PCR (RT-PCR) was performed for SNP genotyping analysis (single nucleotide polymorphisms) on candidate genes. As secondary endpoint we evaluated imatinib, dasatinib and nilotinib intracellular PK by HPLC tandem Mass Spectrometry detection validated method [4]. Potential impact of genetic polymorphisms of the same genes on the TKIs intracellular levels was also evaluated. All patients enrolled in the study signed a consent for the collection of 1 Heparin tube of whole blood for plasma PK analysis and DNA extraction for PG analysis, and 4 EDTA tubes of whole blood for peripheral blood mononuclear cell (PBMC) isolation finalized to intracellular PK analysis. Samples collection started in January 2010 and will finish within three years.

Here we present first results on analyses conducted on 46 CML patients in therapy with TKIs, by samples collection lasted 15 months. Briefly, we observed that genetic factors could affect patients response to therapy by influencing drugs intracellular and plasmatic concentrations. Major results were obtained for dasatinib, the drug, among all TKIs analyzed, most concentrated in cells compared to plasma compartment concentration. Intracellular concentration of dasatinib, furthermore, seems to be strongly affected by the P-Glycoproteins polymorphisms.

Future steps will be to finish samples collection and to correlate PG data on patients clinical responses.