Single nucleotide polymorphisms of ABCB1 gene influence on intracellular concentrations of dasatinib.

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Use of BCR-ABL TKIs (Tyrosine-Kinase inhibitors) is the standard therapy for chronic myeloid leukemia (CML). Dasatinib 100 mg once daily (QD) has been registered as first-line treatment for chronic phase CML because it has been shown to be able to elicit faster and deeper cytogenetic and molecular responses than imatinib 400 QD, preventing also some events of progression to advanced phases of the disease. However, very little is at present known about the relationship existing between dasatinib intracellular concentration, as well as about the factors that can influence drug intracellular penetration. This could help in understanding the relationship existing between drug level and its effectiveness in individual patients, as well as it may potentially help to modulate drug level by dose adjustment, useful to prevent toxicity and unwanted side-effects that could limit dasatinib efficacy. Aim of our study was to perform quantification of dasatinib in human peripheral blood mononuclear cells (PBMC) and evaluated whether single-nucleotide polymorphisms (SNPs) in ABCB1 gene may work as predictors of dasatinib exposure. Patients administered with dasatinib since at least 1 month were considered in the study. Dasatinib PBMC level was measured in samples by validated High Pressure Liquid Chromatography tandem MS detection methods (D'Avolio 2012, De Francia 2009). Genotyping analysis was conducted by real time PCR based allelic discrimination using standard methodology. Twelve patients met the inclusion criteria. Despite the low number of patients, significant correlations between PBMC concentrations and PBMC concentrations/dose and ABCB1 SNPs 3435C>T and 1236C>T were observed. Specifically, the median intracellular dasatinib Ctrough in individuals with homozygote mutation allele for 1236C>T was lower as compared to patients with wild-type(WT)/heterozygote(ET) genotype [599 (±271) vs 1436 (±1670), respectively, p=0.042]. Similarly, intracellular dasatinib concentrations in individuals with homozygote mutation allele for 3435TT and 2677TT were lower as compared to patients with WT/ET genotype, with no significant p-value [673 (±324) vs 1436 (±1692), p=0.089; 673 (±54) vs 1256 (±1599), p=0.390, respectively], but with a clear trend. This data were significant when intracellular concentrations were corrected with each patient dosage of dasatinib. When we considered patient carriers of at least a homozygote mutation (TT carrier) on SNPs examined, intracellular concentrations have been shown to be significantly lower than WT/ET patients [599 (±313) vs 1559 (±1706), p<0.001, respectively]. In conclusions, these findings suggest that ABCB1 SNPs may actually influence PBMC drug exposure. Since the drug fraction reaching the intracellular compartment is the one exerting therapeutic action, these factors could act on the response to therapy as well as on the onset of some toxicity effects. Further clinico-pharmacological studies, with an higher number of patients, are now required to confirm this association and to establish a relationship between this SNP of the ABCB1 gene and response and side effects observed in individual patients during dasatinib therapy.

D'Avolio (2012). *J Pharm Biomed Anal.* 59, 109-116.
De Francia (2009). *J Chromatogr B Analyt Technol Biomed Life Sci.* 877, 1721-1726.