The pharmacogenetics of tyrosine-kinase inhibitors in chronic myeloid leukemia: is there enough room for epigenetics?

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The chronic myeloid leukemia (CML) has been the first haematological disease that benefited from a targeted therapy with imatinib, a BCR-Abl tyrosine-kinase (TKIs). Since then, a number of other drugs, such as nilotinib, dasatinib, bosutinib and ponatinib, have been introduced in clinical settings as second- or third-line therapeutic options. However, clinical efficacy and tolerability may significantly differ in some patients. Therefore, a number of studies have been focused on pharmacogenetics (i.e., polymorphisms and gene expression) of proteins that are involved in transport across membranes and metabolism of TKIs in CML patients. Although the efforts in that field, an uncertainty still remains for single nucleotide polymorphisms (SNPs) as predictive biomarkers of drug efficacy and/or tolerability. In order to fill the gap and the discrepancies observed in some studies, a possible solution could be the evaluation of epigenetic factors, such as the Polycomb group genes (PcGs). PcG members are organized in two multimeric Polycomb Repressive Complexes (PRC1 and PRC2). The coordinated activity of those protein complexes may control cell proliferation by silencing target genes and, as a consequence, the effect of antineoplastic drugs. BMI1 is a PRC1 member that acts trough the modulation of gene transcription of several downstream targets. Interestingly, BMI-1 is a downstream target of BCR-Abl and its expression is becoming higher when CML evolves from the chronic up to the accelerated/blastic phase. These observations suggest that the interplay between BCR-Abl and BMI1 is fundamental for the disease and the evaluation of BMI1 expression may be an useful prognostic marker. Therefore, the aim of the study was to evaluate the expression of BMI1 in CML patients before and during the administration of imatinib. The study has been approved by the Ethics Local Committees (Pisa and Vancouver, BC, Canada) within the coordinated research activity of the TIKlet protocol (NCT01860456).
Thirthy CML patients were enrolled after giving their informed consent. Bone marrow samples were obtained at diagnosis, before the beginning of imatinib administration, and 3 months after. Those samples were then used to extract and to reverse transcribe the total mRNA. The cDNA was analysed by SYBR green primers and the relative BMI1 gene expression was normalized by GAPDH expression that was used as a reference gene. Expression levels were calculated by the -2DDCt method. At the same time points, 20 ml of peripheral blood were obtained to extract total mRNA for the analysis of BCR-Abl1/Abl1 International Scale (IS) ratio in order to score molecular response (MR) of patients according to the most recent international guidelines. Finally, haematological and cytogenetic responses (CyR) were scored, and, together with MR, they have been compared with BMI1 levels of expression among the enrolled patients.
The gene expression evaluation in patients returned detectable levels of BMI1 mRNA in all of the samples (median value and range, 21.2 and 1.0-55.8). No significant correlations were observed between the variation in gene expression levels before and after imatinib and the cytogenetic assay. However, irrespective to the cytogenetic data, BMI1 was significantly upregulated after 3 months of treatment. More interestingly, those patients who had the highest upregulation of BMI1 expression required a longer time to achieve a MR3 (i.e., a reduction in IS score down to 0.1% with respect to baseline; 22 months vs. 11 months, p=0.06). These results seem to confirm an association between BMI1 upregulation and a lower sensibility of Phildelphia-positive leukemia cells toward TKIs and further studies are warranted.
In conclusion, the evaluation of PcG members could shed new light on the role of epigenetic factors, alone or in association with other pharmacogenetic markers, for imatinib efficacy against CML and, possibly, second generation TKIs such as nilotinib.