Therapeutic drug monitoring of imatinib

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In this issue of the *Revista Brasileira de Hematologia e Hemoterapia*, Martins et al.[1] are publishing an interesting review, a meta-analysis, of the clinical and analytical aspects of therapeutic drug monitoring of imatinib in chronic myeloid leukemia (CML).

Imatinib, the archetype for tyrosine kinase inhibitor therapeutics, is an excellent example of intelligent drug development accompanied by growing therapeutic drug monitoring (TDM). It is the current standard of care in the treatment of CML as it induces durable responses and prolonged survival. Martins et al. should have mentioned that imatinib is also recommended in the treatment of gastrointestinal stromal tumors (GISTs) for its exceptional activity in inhibiting the constitutively active conformation of the KIT and PDGFRA genes found in the majority of patients with this disease.[2,3]

Plasma imatinib levels were frequently unrelated to the daily administered dose of imatinib. It is well established that imatinib, similar to many other drugs, produces significant interindividual pharmacokinetic variability and as a consequence, plasma exposure to the drug from a given dosing regimen can vary widely among patients. The causes of such variability may be related to several factors including

– environmental factors and diseases (food, liver function, abnormal clearance volume, protein contents, etc.)[4]

– drug interactions (cytochrome inducers or inhibitors)

– genetic polymorphisms (mainly CYP3A5, but also CYP2D6, CYP2C9 or CYP2C19, influx or efflux transport proteins, such as OCT1, OCTN2, OATP1A2, OATP1B3, and ABCB1 or ABCG2, respectively)[5]

– lack of compliance

In both diseases, a good and statistically significant pharmacokinetic-pharmacodynamic relationship has been reported by several studies with better outcomes when plasma imatinib levels are kept above a defined cut-off point. The most frequent pharmacodynamic biomarkers used to assess treatment efficacy are complete cytogenetic response (CCR), complete molecular response (CMR) and major molecular response (MMR). A general consensus has been reached that suggests that 1000 ng/mL is the minimal plasma concentration of imatinib.[6,7] The definition of the upper therapeutic concentration is less clear as the drug does not appear to cause severe side effects and long-term effects have not been ascertained yet. Some authors have suggested an interest for imatinib free fraction determination, corresponding to the active fraction reaching target cells.[3] Patient selection and frequency of analyses should be better determined. But questions remain such as should plasma drug determination be performed early after the onset of treatment in order to prevent therapeutic failure and the occurrence of side effects, or should it be limited to patients with unexpected absence of clinical response or toxicity? Could the pharmacogenetic analyses – by identifying drug disposition profiles – contribute to a reduction in plasma drug analyses? Should we measure free plasma concentration? Further studies are obviously needed to find a response to these questions.

In their review, Martins et al.[1] correctly identified some potential causes impacting on the benefit of imatinib TDM:

i) Heterogeneous and erratic sampling times could be a serious limitation in the interpretation of the data that affects TDM efficacy. An improvement in the sampling time flexibility and in prediction of the robustness of pharmacokinetics is needed and may be obtained by a mathematical algorithm or by population pharmacokinetics with Bayesian estimators.

ii) Non-consistent results with poorly validated analytical methods should also be considered another cause of misinterpretation. The only analytical techniques available are based on chromatographic separation with two possible detection methods (ultra-violet or mass-spectrometry). It is generally admitted that liquid chromatography with mass spectrometric detection (LC-MS) is superior to the liquid chromatography with ultra-violet detection (LC-UV), both for sensitivity and specificity reasons. However, it must be clear that an analytical method based on mass spectrometry can by no means be, by definition, a reference method. Similarly to any other analytical method, mass

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spectrometry can be graded from inadequate to gold standard, depending upon the effort given during the development and validation steps.[8] LC-MS has the potential to be superior to LC-UV but is limited by the costs of the instrument, as mentioned by Martins et al.[1] and by the expertise required.

Although there is evidence of interest in imatinib TDM, this still remains limited to a few centers for several reasons. CML and GIST are rare diseases and imatinib measurement will never become a common assay and thus may not interest large diagnostic companies to produce automated assays. Imatinib TDM may appear erroneously unnecessary because the drug's toxicity is moderate and the importance in optimizing the drug efficacy may be underestimated. TDM always represents constraints and costs both for the nursing staff (accuracy of the sampling time, etc.) and for the patient (necessity to reach a medical centre for drawing blood). For large countries such as Brazil, distances to medical centers may represent an important limitation for TDM. Dry blood spot sampling, easily mailed to the medical laboratory, could be an alternative and attractive approach to be considered. Finally, the availability of chromatographic equipment and expertise also represents a limitation to a widespread use of imatinib TDM. Martins et al. already emphasized the advantage of UV detection over mass spectrometric detection for obvious financial reasons.

From all the considerations stated above, we agree with Martins et al. and feel that imatinib TDM should provide added value to the optimization of this therapy. Enough evidence is reported in the literature and it should be the responsibility of each country's health authorities – maybe together with the pharmaceutical industry – to promote access through a specialized central-laboratory network able to manage adequately this activity.

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