An alternative analytical method for the therapeutic drug monitoring of irinotecan: toward personalized medicine

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Background: Standard BSA-based dosing of chemotherapy does not take into account the many inter-patient differences that make drug exposure highly unpredictable, leading to a significant variability in both therapeutic and toxic effects of anticancer drugs. This has led clinicians and researchers to consider the uniqueness of each patient, paving the way to the so called *personalized medicine*. In this context, therapeutic drug monitoring (TDM) is intended to individualize the drug dosages or schedules by the measurement and interpretation of drug concentrations in biological fluids. Anyway, its limited application in clinical practice is due to several complications. For instance, the pharmacokinetic analyses are commonly performed with analytical methods based on liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS), which are time consuming and require a high operator expertise. On this background, an AIRC5x1000 project has been founded with the purpose to develop alternative analytical strategies for TDM in order to improve the application of this approach in clinical routine.

Aims: The aim of this study was to demonstrate the clinical applicability of a newly developed MALDI-TOF method to perform quantitative analysis of irinotecan for TDM. Irinotecan, a widely used antineoplastic drug mostly employed for the treatment of colorectal cancer, is a feasible candidate for TDM due to the presence of a wide inter-individual variability in the pharmacokinetic and pharmacodynamic parameters. In order to demonstrate that the MALDI-TOF method can offer quick and accurate results suitable for TDM, we cross validated it, according to FDA/EMA guidelines, in comparison with a standard LC-MS/MS method, actually applied in a genotype guided phase I study conducted by our group.

Materials and methods: For the cross-validation, the same plasma samples from patients with metastatic colorectal cancer enrolled in the clinical study were analysed in blind by both the analytical assays. The MALDI-TOF method can be considered validated if the difference between the values obtained with the two methods results within 20% for at least 67% of the repeats.

Results: The newly developed MALDI-TOF method has been successfully validated according to FDA-EMA guidelines. Standard curves for irinotecan were linear ($R^2 \geq 0.9842$) over the concentration ranges between 300-10000 ng/mL and showed good back-calculated accuracy and precision. Intra- and inter-day precision and accuracy, determined on three concentrations levels were always <12.8% and between 90.1% and 106.9%, respectively. A total of 108 plasma samples from patients enrolled in the genotype-guided phase I study of irinotecan have been quantified with the MALDI-TOF method. The cross validation procedure showed a good reproducibility between the two methods, being the percentage differences within 20% in more than 70% of the total amount of clinical samples analysed.

Conclusions: The interesting novelty of this fast method based on MALDI-TOF is its applicability in clinical routine analysis, such as TDM. In fact, it does not require any chromatographic run, thus saving time and reducing the amount of organic solvents consumed, and it requires only few microliters of samples for the analysis. These results demonstrated that MALDI-TOF is a helpful tool for quantifying drugs in real time, allowing, for instance, the study of irinotecan pharmacokinetics during the drug infusion time (2 h) providing important information about the actual drug levels.