Poster

[P25-9] P25-9: Oncologic drugs (1)

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[P25-9-3] Quantification of hydroxyurea in human plasma by HPLC-MS/MS and its application to pharmacokinetics in patients with chronic myeloid leukaemia

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Background

Hydroxyurea (HU) has been used in the treatment of chronic myeloid leukaemia (CML) and other myeloproliferative malignancies. Considering patient’ s wide variation in clinical response to HU, a new and simple liquid chromatography-tandem mass spectrometry (LC-MS/MS) method was developed and validated to monitor patients’ compliance to treatment and investigate the pharmacokinetics of HU in patients with CML.

Methods

Plasma samples were treated with acetonitrile to precipitate protein. The supernatant was injected directly without derivatization and separated on a hydrophilic interaction liquid chromatography column. HU was quantitatively analyzed with a mobile phase of acetonitrile-1.5 mM ammonium formate (90:10, V:V) within 3 min. Stable isotope labeled HU-$^{13}C_1$, $^{15}N_2$ was used as internal standard.

Results

The proposed method provided a linearity range of 1-200 g/mL. The coefficients of variation for intra- and inter-day precision were less than 2.07% and 4.28%, respectively, while the accuracy (bias) was in the range of -3.77-2.96%. This method was satisfactorily applied to the determination of HU in two patients with CML. The maximum plasma concentration (C_{max}) of patient A and B was 39.0 and 85.5 g/mL, while the time of C_{max} was 1.2 and 0.3 h, reapectively. Total clearance of patient A and B was 10.13 and 6.74 L/h. Apparently, patient A exhibited slow oral absorption, indicating longer dosing interval or lower dosage might be needed. Oppositely, patient B showed fast absorption, indicating shorter dosing interval or higher dosage could be appropriate.

Conclusions

This method applied a HILIC column to measurement of HU in human plasma, proved to have sufficient sensitivity, better specificity, and reproducible linearity. This novel analytical method is highly feasible for HU pharmacokinetic studies and routine drug monitoring in patients with CML.

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