Quantification of midostaurin in plasma and serum by stable isotope dilution liquid chromatography-tandem mass spectrometry: Application to a cohort of patients with acute myeloid leukemia

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Background
Midostaurin is an oral multitargeted tyrosine kinase inhibitor for the treatment of acute myeloid leukemia (AML). Therapeutic drug monitoring of midostaurin may support its safe use when suspecting toxicity or combined with strong CYP3A4 inhibitors.

Methods
A stable isotope dilution liquid chromatography–tandem mass spectrometry method was developed and validated for the determination and quantification of midostaurin in human plasma and serum. Midostaurin serum concentrations were analyzed in 12 patients with FMS-like tyrosine kinase 3 (FLT3)-mutated AML during induction chemotherapy with cytarabine, daunorubicin, and midostaurin. Posaconazole was used as prophylaxis of invasive fungal infections.

Results
Linear quantification of midostaurin was demonstrated across a concentration range of 0.01–8.00 mg/L. Inter- and intraday imprecisions of the proposed method were well within ±10%. Venous blood samples were taken in nine and three patients in the first and second cycle of induction chemotherapy. Median (range) midostaurin serum concentration was 7.9 mg/L (1.5–26.1 mg/L) as determined in 37 independent serum specimens.

Conclusions
In a real-life cohort of AML patients, interindividual variability in midostaurin serum concentrations was high, highlighting issues concerning optimal drug dosing in AML patients. A personalized dosage approach may maximize the safety of midostaurin. Prospective studies and standardization of analytical methods to support such an approach are needed.

Keywords
AML, CYP3A4, LC–MS/MS, midostaurin, posaconazole, therapeutic drug monitoring