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Liquid chromatography–tandem mass spectrometry assay for therapeutic drug monitoring of the tyrosine kinase inhibitor, midostaurin, in plasma from patients with advanced systemic mastocytosis

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ABSTRACT

We developed and validated quantitative bioanalytical liquid chromatography–tandem mass spectrometry assay for the protein kinase inhibitor, midostaurin. Plasma samples were pre-treated using a protein precipitation with methanol containing midostaurin-d_5 as an internal standard. After centrifugation, 5 μL of the supernatant was injected into the chromatographic system. The system consisted of a 3.5 μm particle bonded octadecyl silica column, with gradient elution using a mixture of 0.1% (v/v) formic acid in acetonitrile and 10 mM ammonium formate in water with 0.1% formic acid. The analyte was quantified using the selected reaction-monitoring mode of a triple quadrupole mass spectrometer equipped with a heated electrospray interface. The assay was validated in a 75–2500 ng/mL calibration range. For quality control, within-day and between-day precisions were 1.2–2.8%, and 1.2–6.9%, respectively. The β-expectation tolerance limit (accuracy) met the limits of acceptance ±15% (±20% for the LLQ). The drug was sufficiently stable under all relevant analytical conditions. The assay has successfully been used to assess drug levels for therapeutic drug monitoring in patients presenting advanced systemic mastocytosis and treated with the promising midostaurin.

1. Introduction

Advanced systemic mastocytosis (SM) and, especially aggressive systemic mastocytosis (ASM) or mast cell leukemia (MCL) with or without associated clonal hematological Non-Mast-Cell Lineage Disease (AHNMD) still have a very poor prognosis with an overall survival of 41 months in ASM, 2 months in MCL, 24 months in MS-AHNMD [1]. No standard care is yet available due to constant suboptimal response to various therapies including high dose chemotherapy and, imatinib since the very high frequency of naturally resistant KITD816V-mutated patients. Among tyrosine kinase inhibitors, midostaurin (*N*-benzoylstaurosporine, also known as PKC412 or CGP41251, shown in Fig. 1) takes place in the treatment of those patients. Midostaurin is a powerful inhibitor of several proteins including the protein kinase C (PKC) isoforms, the tyrosine

Abbreviations: AHNMD, associated clonal hematological non-mast cell lineage disease; ANSM, Agence Nationale de Sécurité du Médicament et des produits de santé; ASM, aggressive systemic mastocytosis; CEREMAST, Centre de Référence des Mastocytoses; DMSO, dimethylsulfoxide; HESI, heated electrospray ionization; IS, Internal Standard; LLQ, lower limit of quantification; MCL, mast cell leukemia; QC, quality control; RSD, Relative Standard Deviation; SM, systemic mastocytosis; SRM, selected reaction monitoring; TDM, therapeutic drug monitoring; TKI, tyrosine kinase inhibitor; TUA, temporary use authorization; VEGFR, vascular endothelial growth factor receptor.

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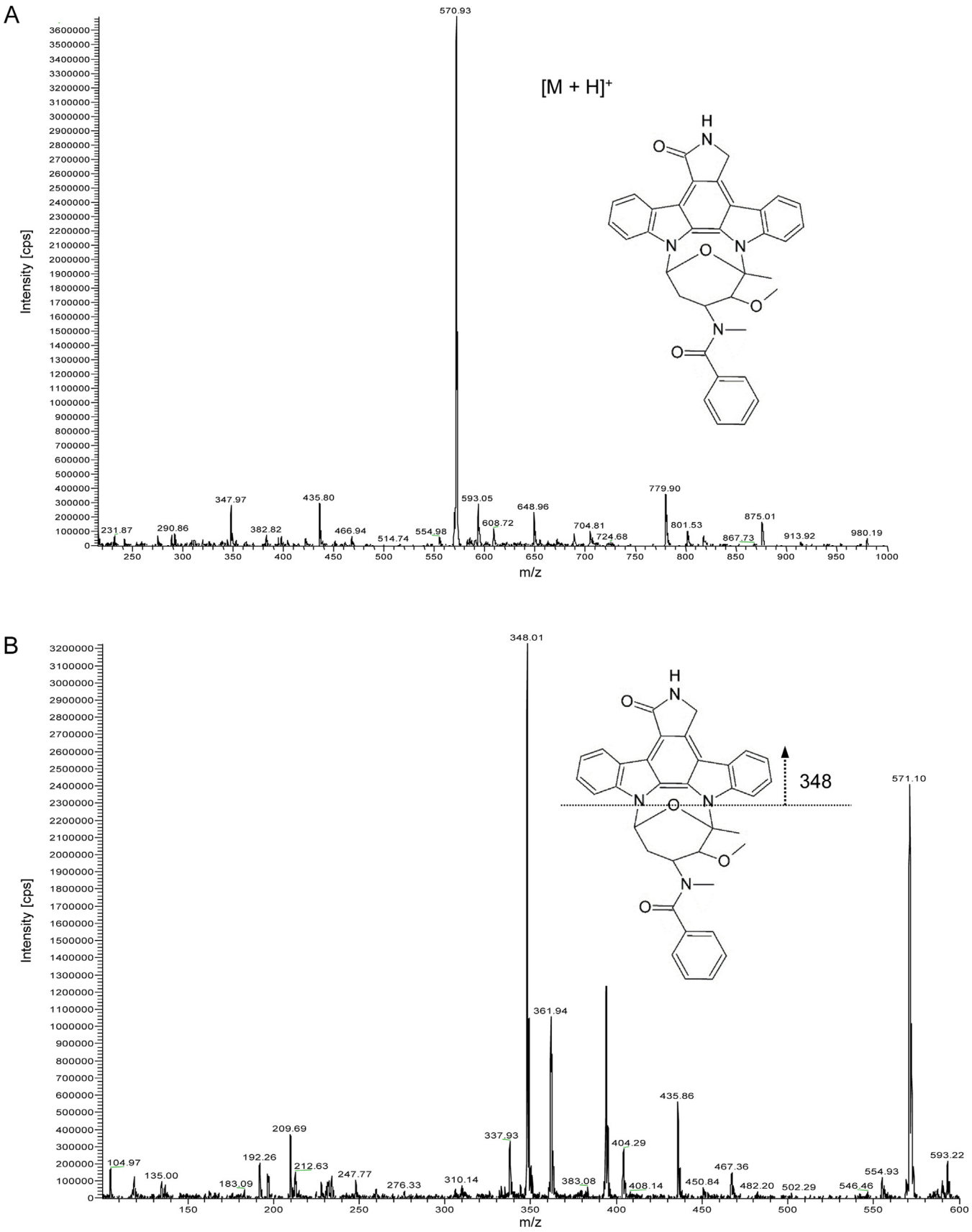

Fig. 1. Electrospray spectrum (A) at *m*/*z* 571.1 and product spectrum (B) at *m*/*z* 348.0 at −23 V of midostaurin, mass spectrometric conditions are as used in the reported bioanalytical assay without using SRM.