Role of Cytochrome P450 3A4 and 1A2 Phenotyping in Patients with Advanced Non-small-Cell Lung Cancer Receiving Erlotinib Treatment

Zinnia P Parra-Guillen, Peter B Berger, Manuel Haschke, Massimiliano Donzelli, Daria Winogradova, Bogumila Pfister, Martin Früh, Silke Gillessen Sommer, Stephan Krähenbühl, Charlotte Kloft & Markus Joerger

Erlotinib is metabolized by cytochrome p450 (CYP) 3A and CYP1A. This study assessed CYP3A4 (midazolam) and CYP1A2 (caffeine) phenotyping in plasma and dried blood spots (DBS) for predicting the pharmacokinetics and toxicity of erlotinib in 36 patients with advanced NSCLC. On day 1, erlotinib 150 mg OD was initiated, and the two oral probe drugs midazolam (2 mg) and caffeine (100 mg) were added on day 1. Plasma and DBS were collected for erlotinib, OSI-420 and probe drugs for up to 6 hr on day 1 and 2-weekly up to week 10. Probe drugs, erlotinib and OSI-420 were analysed using LC-MS-MS, and PK data were processed using population modelling. A high correlation was found between plasma and DBS concentrations for erlotinib (R² = 0.960, p < 0.0001), OSI-420 (R² = 0.971, p < 0.0001), midazolam (R² = 0.995, p < 0.0001) and caffeine (R² = 0.968, p < 0.0001). Apparent oral caffeine clearance was significantly correlated with erlotinib clearance (R² = 0.33, p = 0.048), while midazolam clearance was not (R² = -0.09, p = 0.596). Erlotinib clearance was lower in patients experiencing grade 2 or 3 rash as compared to patients experiencing grade 0 or 1 rash (3.15 versus 3.93 L/hr, p = 0.086 for Student's t-test). The results suggest that probe drug phenotyping is unlikely to substitute therapeutic drug monitoring of erlotinib in patients with advanced NSCLC, but erlotinib PK sampling from DBS may replace more invasive venous sampling and facilitate TDM in patients with cancer.