

TITLE: Mechanism-based Population Pharmacokinetic Model of Oxaliplatin in Cancer Patients

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BACKGROUND/OBJECTIVES: Oxaliplatin is a novel platinum derivative approved for the treatment of patients with advanced colorectal cancer. The objective of this study was to develop a mechanism-based PK model that explained the concentration-time profiles of plasma ultrafiltrate and plasma protein-bound platinum after oxaliplatin administration to cancer patients. In addition, exposure-toxicity relationships using this new PK information were also investigated.

METHODS: Thirty-four cancer patients with impaired renal function were included in the data analysis. Patients were treated with 60 to 130 mg/m² of oxaliplatin infused over 2 hrs every 3 weeks. PK samples were analyzed for platinum in plasma and plasma ultrafiltrates using ICP-MS techniques. A Monte-Carlo Parametric Expectation Maximization algorithm was used to develop the model and to obtain population parameter estimates. The model was fit to both plasma ultrafiltrate and plasma protein-bound platinum concentrations simultaneously. The logistic regression analysis was used to explore the relationships between exposure and toxicity of oxaliplatin.

RESULTS: In the final model, measured plasma ultrafiltrate platinum is partitioned into active/free and inactive/low molecular weight ultrafiltrate (LMW-ULF) platinum species (Figure 1). The active/free platinum presents immediately after oxaliplatin administration is cleared from plasma ultrafiltrates by protein binding, tissue distribution/degradation, and by chemical reactions with plasma constituents that ultimately form inactive/LMW-ULF platinum species. These LMW-ULF platinum species can bind irreversibly to plasma proteins to form a drug-protein complex. The LMW-ULF platinum is slowly released back into the systemic circulation following degradation of these drug-protein complexes. The final model well described the time-course of measured plasma ultrafiltrate and plasma protein-bound platinum concentration following oxaliplatin administration (Figure 2) and it explained the complex time-dependent nonlinear relationship between the plasma ultrafiltrate and plasma protein-bound platinum. Exposure-toxicity analyses suggest that model predicted cumulative exposure to active/free plasma ultrafiltrate platinum but not to inactive/LMW-ULF or plasma protein-bound platinum is associated with peripheral sensory neuropathy in oxaliplatin-treated cancer patients.

CONCLUSIONS: To our knowledge, this is the first mechanism-based comprehensive population PK model of oxaliplatin developed that increases our understanding of the complex pharmacology of oxaliplatin in cancer patients. The model can simultaneously describes both the measured plasma ultrafiltrate and plasma platinum concentration profiles and it explains the complex relationship between these two measured platinum species in cancer patients.

REFERENCES:

1. Takimoto CH, Graham MA, Lockwood G, Ng CM, et al. Clin Cancer Res 2007;13(16):4832-9
2. Graham MA, Lockwood GF, Greenslade D, Silvano B, et al. Clin Cancer Res 2000;6:1205-8

Figure 1. Schematic representation of the final model of oxaliplatin in cancer patients

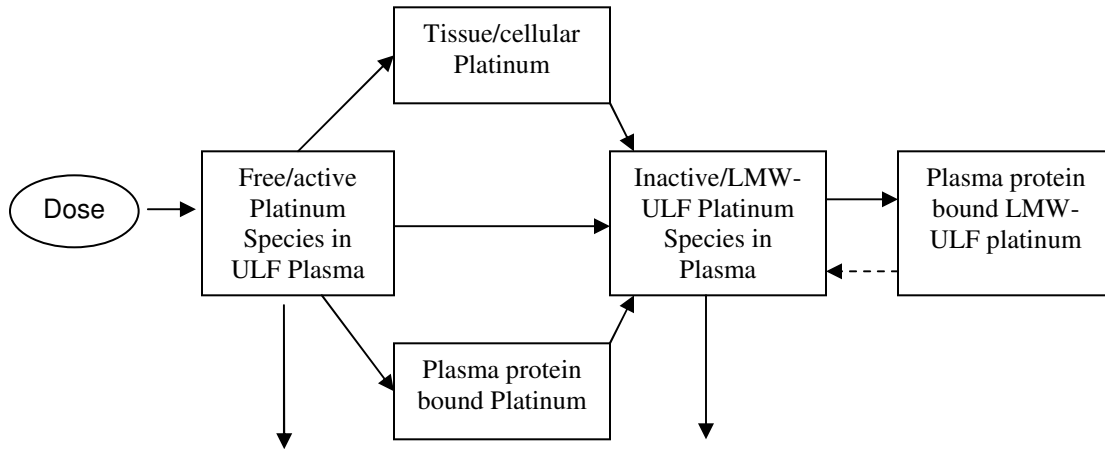


Figure 2. Representative plot of the individual observed and model predicted plasma ultrafiltrate and protein-bound plasma platinum concentrations of oxaliplatin in cancer patients.

