Pharmacokinetics of lenalidomide during high cut-off dialysis in a patient with multiple myeloma and renal failure

Online resource 1:

Kim Dao (Kim.Dao@chuv.ch)[1], Yimin Lu (Yimin.Lu@unil.ch)[2], Cody J. Peer (cody.peer@nih.gov)[3], William D. Figg (wf13e@nih.gov)[3], Raphael Stadelmann (Raphael.Stadelmann@chuv.ch)[4], Michel Burnier (Michel.Burnier@chuv.ch)[2], Thierry Buclin (Thierry.Buclin@chuv.ch)[1], Sebastien Kissling (Sebastien.Kissling@chuv.ch)[2]

Authors affiliations:

1) Division of Clinical Pharmacology, Biomedicine, Department of Laboratories, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland.

2) Service of Nephrology, Department of Medicine, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland.

3) Clinical Pharmacology Program, Center for Cancer Research, National Cancer Institute, Bethesda, Maryland, USA.

4) Division of Hematology, Department of Oncology, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland.

Lenalidomide pharmacokinetic model development:

A pharmacokinetic (PK) model was developed to predict plasma concentrations of lenalidomide during HCO dialysis, using published lenalidomide PK parameters, the patient's renal status on admission and the dialysis settings. [1-3] A PK model was built up initially without taking into account our observations, and then compared to the observed plasma concentrations, to check whether they were consistent with the model.

One compartment kinetics best described lenalidomide disposition according to the literature. Lenalidomide normal total clearance ($CL_{Tot,N}$), non-renal clearance (CL_{NR}), volume of distribution (V), unbound fraction (f_u), and time of peak concentration (t_{max}) were obtained from the literature, as follows: $CL_{Tot,N}$ = 11.8 L/h; CL_{NR} = 2.3 L/h; V = 0.77 L/kg; f_u = 0.56; t_{max} = 1.25 h. Note that CL and V are apparent values, incorporating bioavailability.

The patient's renal function (GFR) was estimated at 2.5 mL/min (i.e. 0.15 L/h). Lenalidomide normal renal clearance ($CL_{Tot,N}$ - CL_{NR}) was proportionally reduced according to the ratio of GFR over normal creatinine clearance (6 L/h):

$$CL_{R,patient} = (GFR / 6) \cdot (CL_{Tot,N} - CL_{NR}) \quad (1)$$

Lenalidomide dialytic clearance (CL_{Dial}, L/h) was estimated based on blood flow (Q_{Blood}), unbound fraction (f_u) and blood/plasma concentration ratio (r_{bp}):

$$CL_{Dial} = Q_{Blood} \cdot f_u \cdot r_{bp} \quad (2)$$

The r_{bp} was taken as 1 minus the hematocrit, i.e. 0.77 in the patient, despite the fact that a value of 1 had been published [3]. We considered that erythrocytes had not enough time to equilibrate with plasma during their transit through the filter due to the rate of dialysate flow.

The patient's lenalidomide total clearance $CL_{Tot,patient}$ (L/h) was equated to the sum of the residual renal clearance ($CL_{R,patient}$), non-renal clearance (CL_{NR}) and dialytic clearance (CL_{Dial}):

$$CL_{Tot,patient} = CL_{R,patient} + CL_{NR} + CL_{Dial} \quad (3)$$

An absorption rate constant (k_a) of 0.12 h^{-1} was back estimated using the concentration peak time (t_{max}) from the literature (i.e. 1.25 h) [1].

The predicted concentration C_{pred} (µg/L) of lenalidomide over time was calculated according to the differential equation:

$$\frac{dC}{dt} = \frac{k_a \cdot A_a - CL_{Tot,patient} \cdot C}{V} \quad \text{with } C_{pred} = 0 \text{ at } t = 0 \quad (4)$$

Where A_a is the amount of lenalidomide in the absorption site, calculated over time according to:

$$\frac{dA_a}{dt} = -k_a \cdot A_a \text{ with } A_a = \text{dose (µg) at } t = 0 \quad (5)$$

The area under the curve (AUC) was calculated over 24 hours as:

$$AUC = \int_0^{24h} C \cdot dt \quad (6)$$

Lenalidomide extraction coefficient (E) was calculated from pre-filter (C_a) and post-filter (C_v) concentrations of lenalidomide measured during HCO dialysis:

$$E(\%) = \frac{(C_a - C_v)}{C_a} \cdot 100 \qquad (7)$$

The predictions based on this model were compared with the observed concentrations. The model was further refined by revising CL_{NR} to 1.44 L/h, V to 0.38 L/kg, f_u to 0.46 and k_a to 60 h^{-1} in order to improve the model fit and to obtain a likely description of lenalidomide concentrations between and during HCO dialysis sessions (Fig. 1). The model was implemented and optimized using Microsoft Excel 2007 (Microsoft Corp., Redmond, WA) with the Solver™ add-on. Sparse PK data does however not allow appropriate estimates of V and k_a. The estimated AUC_{24h} amounted to 3273 µg·h/L for a dosage of 5 mg b.i.d. Lenalidomide extraction coefficient (E) was 53% during the first HCO dialysis and 23% during the second one (Tab. 1). These values are consistent with both our initial estimation of $fu \cdot r_{bp}$ (43%) and data already published during intermittent haemodialysis [2].

References

1. Chen N, Lau H, Kong L, Kumar G, Zeldis JB, Knight R, Laskin OL (2007) Pharmacokinetics of lenalidomide in subjects with various degrees of renal impairment and in subjects on hemodialysis. Journal of clinical pharmacology 47 (12):1466-1475. doi:10.1177/0091270007309563

2. Hou J, Du X, Jin J, Cai Z, Chen F, Zhou DB, Yu L, Ke X, Li X, Wu D, Meng F, Ai H, Zhang J, Wortman-Vayn H, Chen N, Mei J, Wang J (2013) A multicenter, open-label, phase 2 study of lenalidomide plus low-dose dexamethasone in Chinese patients with relapsed/refractory multiple myeloma: the MM-021 trial. Journal of hematology & oncology 6:41. doi:10.1186/1756-8722-6-41

3. Chen N, Wen L, Lau H, Surapaneni S, Kumar G (2012) Pharmacokinetics, metabolism and excretion of [(14)C]-lenalidomide following oral administration in healthy male subjects. Cancer chemotherapy and pharmacology 69 (3):789-797. doi:10.1007/s00280-011-1760-3