Background and Objectives:

A model for chemotherapy-induced myelosuppression (Fig. 1, [1]), developed from patient data, showed similar system-related parameters (WBC, MTT and γ) across drugs but the drug-related parameter estimates (Slope) were drug-dependent, as expected. The aim of the present study was to explore if the drug-related parameter estimates are of comparable magnitudes in rats and patients and may be used for predictions of the full time-course of myelosuppression in patients.

Methods:

5-Fluorouracil (5-FU), epirubicin, cyclophosphamide (CP), docetaxel, paclitaxel or etoposide were administered to rats (n=169).

The myelosuppression model [1] was applied to all data simultaneously, Individual or typical population PK parameters were used to predict the drug administration. The analysis was performed using FOCE in NONMEM VI.

Results:

The original myelosuppression model fit the rat data adequately (Fig. 2). The fit improved when a fraction of the Slope was allowed to affect also the other cell types, but to be consistent with the model for patients, the original model was used in the comparison with patients. The MTT was approximately half of the estimate in patients while the feedback parameter was of similar magnitude (Table 1).

The relative difference in Slope estimates for rats and patients [1,2,3] based on total drug concentrations ranged between 28% to 7-fold for the 6 drugs (Fig. 3, left panel).

The relative difference was reduced to ≤37% when correcting for species differences in IC90 ratios in the CFU-GM assay [4] and species difference in protein binding (Fig. 3, right panel).

Conclusions:

The estimated drug-related parameters in rats, patient PK models and typical system-related parameters [1] could successfully be used to predict the time-course of myelosuppression in patients (Fig. 4). Accounting for species differences in protein binding and in vitro sensitivity improved the predictions. This scaling approach might also be useful to early in development predict combination therapies and schedule dependence of myelosuppression.

References: