An Adaptive Dosing Tool For Etoposide Using Neutrophil Counts Based on a Semi-Physiological Model

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Summary

A macro for MS Excel has been developed to aid dosing of etoposide based on neutrophil counts. The predictability is similar to NONMEM.

Background

Neutropenia is one of the major challenges in the dosing of anticancer drugs. A previously published semi-physiological model for myelosuppression [1] has successfully been applied for several cytotoxic drugs, one of them being etoposide, a topoisomerase II-inhibitor.

Initial dose level is usually based on body surface area, and if patient experience low blood cell counts the next dose is either postponed or reduced. To individualize the treatment the observed neutrophil counts from the first cycle could be used for dose adjustment in the next cycle, in order to avoid neutropenia, a prolonged treatment interval and/or a suboptimal tumor effect.

The previously suggested semi-physiological model can be used to describe the changes in neutrophil count with time after etoposide dosing [1]. It uses a series of differential equations to describe the chain of events from maturation in stem cell pool to circulating blood cell, a visual description can be seen in figure 1.

Aim

To develop a dosing tool based on a pharmacodynamic model for myelo-suppression, where the user can obtain an adaptive dose for the next treatment cycle from a user-defined nadir and information from neutrophil counts from the first cycle.

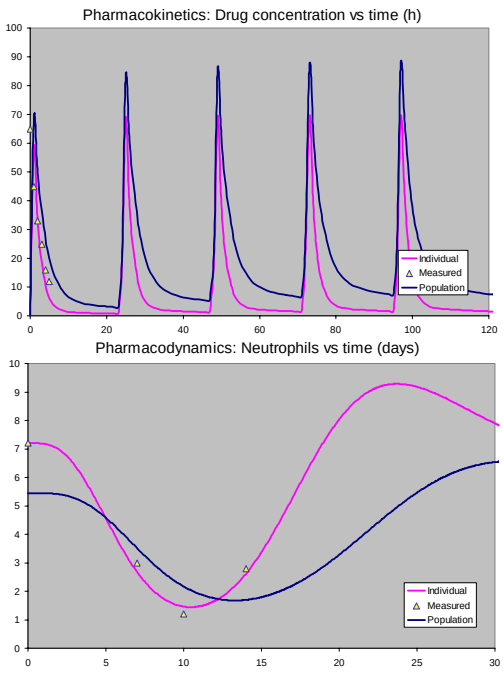

Fig. 2 *Individual and population PK- and PD-profiles of etoposide from the Excel macro as shown to the user*

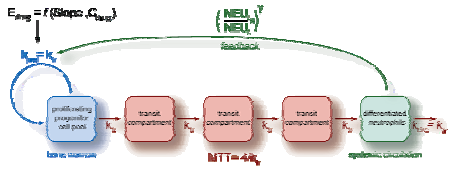

Fig. 1 *Description of the semiphysiological model of myelosuppression*

Methods

To provide a familiar environment for clinicians, MS Excel was chosen as platform. The add-in PopTools (CSIRO, Australia) [2] for Excel was applied to handle the differential equations. Estimates of typical parameters and IIV for etoposide were taken from Toffoli et al [3] for the PK model and Friberg et al [1] for the PD model.

An Excel sheet was designed where the user provide input on dose, concentration and/or neutrophil measurements from the first course. By the click of a button a macro starts a Bayesian process, returning individual estimates on pharmacokinetic and/or pharmacodynamic parameters.

In the next step the user is able to provide a desired target such as a desired nadir or time under a certain neutrophil level. Another macro starts an iteration process returning a suggested dose schedule. Graphic presentation of individual and population mean time profiles are also presented, as seen in figure 2.

Table 1 *Predictive performance of NONMEM and the Excel macro*

	NONMEM		Excel macro	
	MPE	RMSE	MPE	RMSE
Predictions	2.4 %	59 %	3.8 %	60 %
BASE	-0.20 %	12 %	1.7 %	13 %
SLOPE	0.01 %	19 %	2.7 %	21 %
MTT	0.052 %	6.6 %	0.44 %	5.8 %

A comparison of predictive performance between the Bayesian function in the macro to the POSTHOC function in NONMEM was carried out by simulation of 75 individuals receiving five consecutive daily 100 mg 1-hour infusions in two cycles.

In addition to baseline, six measures of neutrophil counts was made in each cycle, and predictions for the second cycle were made only from the simulated PD data from the first cycle. Accuracy and precision was estimated by calculating the mean prediction error (MPE) and root mean squared error (RMSE) [4] both for neutrophil counts in the second course and for the parameters.

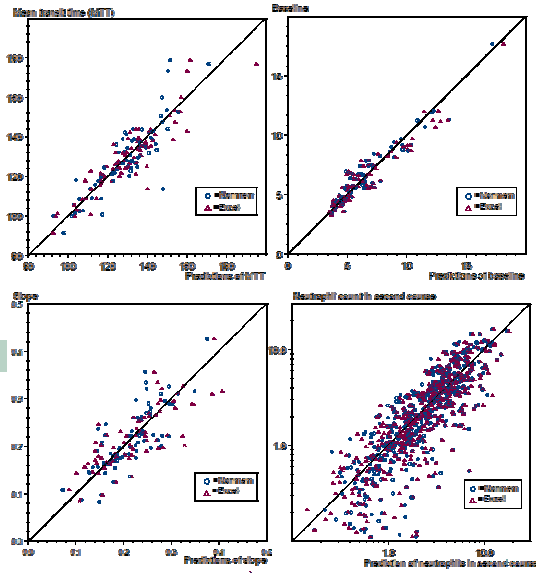

Fig. 3 *Predictions of pharmacodynamic parameters and neutrophil counts*

Results

Three different spreadsheets are now provided by the authors for intravenous dosing of etoposide, using PK-, PD- or PK+PD-information for dose individualization. Computation time is approximately 3 minutes for individual parameter estimation and somewhat shorter for calculation of dose resulting in the desired nadir.

Predictive performance was deemed sufficient in comparison to the POSTHOC option in NONMEM. MPE and RMSE for individual predictions and parameters are shown in table 1. The small differences in the predictions can probably be attributed to differences in the the differential equation solvers.

Conclusions

The tool adequately implements the model, but the user-friendliness and clinical value needs to be assessed in a clinical setting. It is generic and can be adapted for individualization of other drugs. There are also possibilities to include covariate models for the various parameters.

References

[1] Friberg LE *et al. Model of chemotherapy-induced myelosuppression with parameter consistency across drugs.* J Clin Oncol 20:4713–4721, 2002

[2] http://www.cse.csiro.au/poptools/

[3] Toffoli G *et al. Population pharmacokinetics and pharmacodynamics of oral etoposide.* Br J Clin Pharm, 52:511-519, 2001

[4] Sheiner LB, Beal SL *Some suggestions for measuring predictive performance.* J Pharmacokinet Biopharm, 9:503-512, 1981