Toxicity assessment via drug-drug interaction modeling for trabectedin patients with advanced malignancies

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INTRODUCTION. Trabectedin is a DNA minor groove binder, marketed in Europe for the treatment of soft tissue sarcomas and, in combination with liposomal doxorubicin, ovarian cancer. Trabectedin is metabolized mainly by cytochrome P4503A4 (CYP3A4) [1]. A PK study describing the interaction of trabectedin with agents modulating CYP3A4 activity indicates an increased exposure of trabectedin when given with ketoconazole [2]. Our aim is to simulate the potential effects of CYP3A4 inhibitors of different strengths on the incidence and severity of neutropenia following the administration of trabectedin and establish how the dose of trabectedin could be reduced when given concurrently with CYP3A4 inhibitors.

MATERIALS AND METHODS. An approach proposed by Ohno et al [3] was reverse engineered to define the proportion of the CYP3A4 contribution to the metabolization of trabectedin based on the available PK study [2]. The same approach was used –based on available population PK and PK-myelosuppression nonlinear mixed effect models [4,5] – to simulate the effect of CYP3A4 inhibitors of different strengths: ranitidine (mild), diltiazem (moderate), and itraconazole (strong). For each scenario, 900 virtual patients were simulated with the aid of R, SimulX and Shiny, investigating also possible dose reductions.

$$\frac{AUC^*}{AUC} = \frac{CL}{CL^*} = \frac{1}{1 - CR_{CYP3A4} \cdot IR_{CYP3A4}} \quad (1)$$

$$\mathrm{Y} = \ln\left(\frac{AUC^*}{AUC}\right) \sim N(0.506, 0.0335) \quad (2)$$

$$CR_{CYP3A4} = 1 - \frac{1}{\exp(Y)} \quad (3)$$

Computation of CYP3A4 proportion to metabolization. Equation (1) is the formula introduced by Ohno et al in [3] to relate the AUC (or clearance, CL) obtained with the drug alone and the AUC (or clearance) obtained with the coadministration of inhibitors (AUC^*, CL^*) to the proportion of the CYP3A4 contribution to the metabolization of trabectedin (CR_{CYP3A4}) and to the inhibition ratio (IR_{CYP3A4}) of the perpetrator. From [2], we derived equation (2); drawing 900 samples of Y, and remembering that the study in [2] was performed with ketoconazole (hence with $IR_{CYP3A4} = 1$), after plugging (2) in (1), we obtain (3), by which we can compute the value of CR_{CYP3A4} for all the virtual patients.

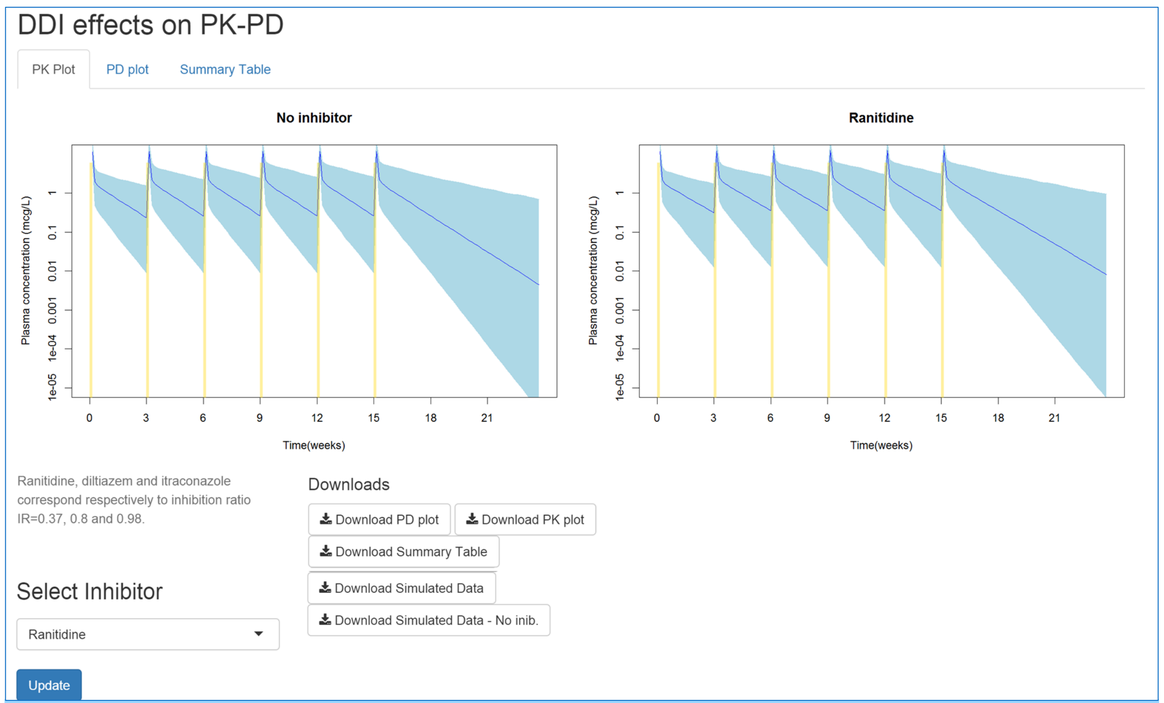

Figure 1: An example of screenshot of the app created with Shiny for the DDI simulations. On the top, below the title, there are three panels: one for the plots of the percentiles of concentration vs time, one for the plots of the percentiles of absolute neutrophil count vs time and one for a summary table. In the lower left corner, one can select the inhibitor to coadministrate. On the right, bottons to download the outputs (plots, table and simulated data). The «Update» button starts the simulation with the chosen perpetrator.

RESULTS. The simulations indicated that mild or moderate CYP3A4 inhibitors provided a lower increase of the systemic exposure to trabectedin compared to itraconazole (+15% and 38% versus +52% in terms of median AUC). As a consequence, the predicted incidence and severity of neutropenia increased compared to the administration of trabectedin alone (e.g., grade 4 neutropenia episodes increased by 2%, 8% and 11% respectively). The dose reduction necessary in order to avoid the increase in exposure and adverse events depends on whether dexamethasone is administered together with trabectedin or not. With dexamethasone, the dose needs to be reduced by 175, 379 and 464 mcg/m^2, respectively for ranitidine, diltiazem and itraconazole coadministration, while, without dexamethasone, reductions are of 222, 479 and 587 mcg/m^2.

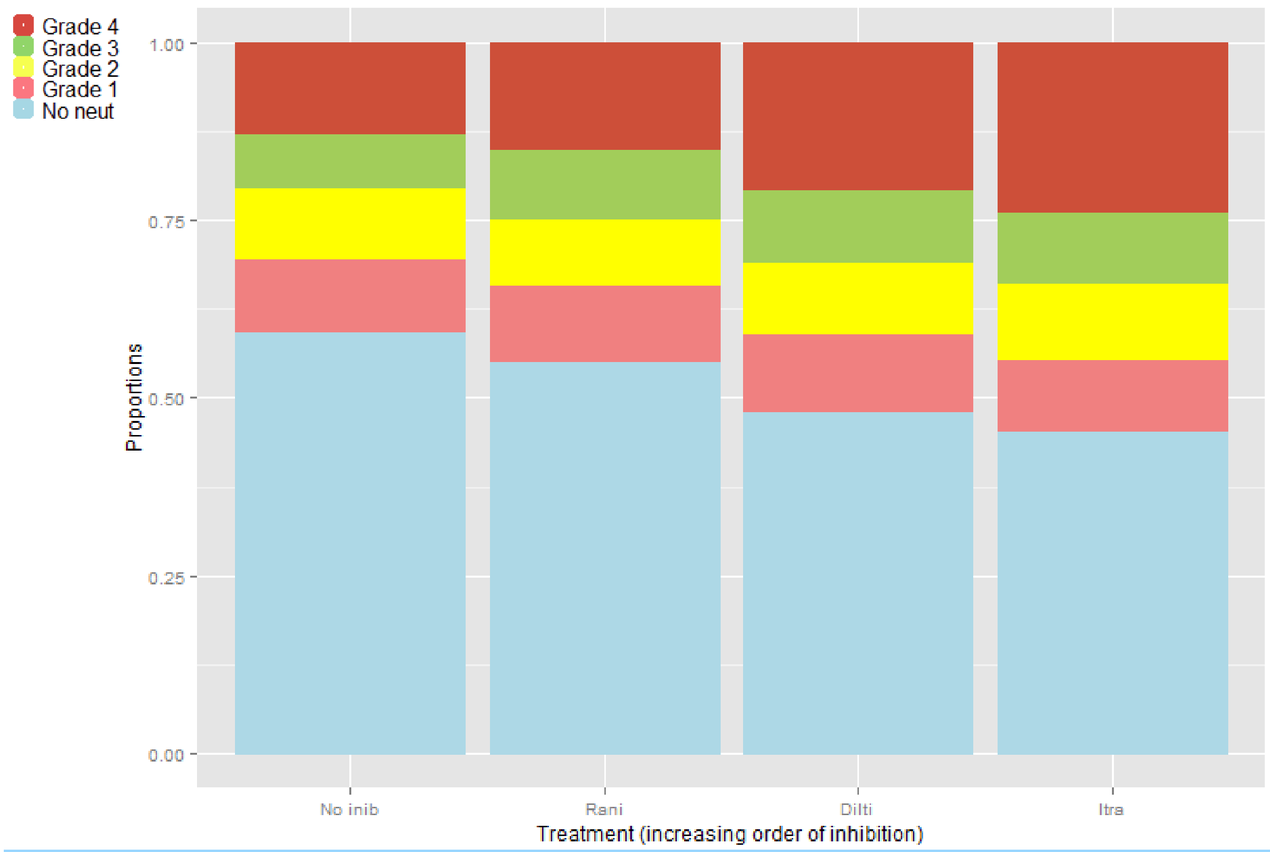

Figure 2: This barplot shows the proportions of patients experiencing different levels of neutropenia: grade 4 (red), grade 3 (green), grade 2 (yellow), grade 1 (pink), as well as no neutropenia events (light blue), in the four scenarios (without inhibitors and with ranitidine, diltiazem and itraconazole co-administration).

	median	*mean*	*Std. dev*	*IC_90*
Opt. dose with ranitidine	1325	1325	10.23808	[1309 , 1343]
Opt. dose with diltialzem	1121	1122	22.13639	[1086 , 1161]
Opt. dose with itraconazole	1035.7	1036	27.11707	[992.9 , 1084.3]

	median	*mean*	*Std. dev*	*IC_90*
Opt. dose with ranitidine	1278	1278	10.97464	[1262 , 1297]
Opt. dose with diltialzem	1020.9	1021	23.72896	[984.5 , 1061.6]
Opt. dose with itraconazole	913.1	913.3	29.06797	[868.5 , 963.0]

Table 1 and 2: The tables contain the statistics (median, mean, standard deviation and 90% confidence interval) of the optimal doses (in mcg/m^2) for ranitidine, diltiazem and itraconazole coadministration, i.e. the doses required in order to have $AUC^* = AUC$.
Top: statistics for virtual patients assuming also dexamethasone. Bottom: statistics for virtual patients not assuming dexamethasone.

CONCLUSIONS. This work exploits a previously published framework [2] in a population PK context to predict the expected PK and PK-PD changes when trabectedin, a CYP3A4 substrate, is given with CYP3A4 inhibitors of different strength, studying trabectedin dose alterations. An analogous approach [6] could be applied to the coadministration of CYP3A4 inducers.

REFERENCES.

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