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 P450 3A4 (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 metabolism of trabectedin based on the available PK study [2]. The same approach was used –based on available population PK and PK-metabolism 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.

\[
\frac{\text{AUC}^*}{\text{AUC}} = \frac{\text{CL}}{\text{CL}^*} = \frac{1}{1 - CR_{\text{CYP3A4}} \cdot IR_{\text{CYP3A4}}} \\
Y = \ln \left( \frac{\text{AUC}^*}{\text{AUC}} \right) \sim N(0.506,0.0335) \\
CR_{\text{CYP3A4}} = 1 - \frac{1}{\exp(Y)}
\]

Computation of CYP3A4 proportion to metabolism. 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 metabolism 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.

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/m², respectively for ranitidine, diltiazem and itraconazole coadministration, while, without dexamethasone, reductions are of 222, 479 and 587 mcg/m².

![Figure 1](image1.png)
![Figure 2](image2.png)

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.
[1] Trabectedin package insert