Accounting for Dose Modifications in Exposure-Response Analyses in Oncology: the Case Example of Brigimadlin

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Objectives

Model-based exposure-response (ER) analyses are a cornerstone of dose optimization in the Project Optimus era of oncology drug development. Yet, during cancer clinical trials, dose modifications (dose interruption, reduction, or discontinuation) are often necessary due to safety and tolerability issues. This leads to feedback in the dose-exposure-safety relationship where safety outcomes have an impact on dose. Failure to account for this feedback in standard model-based ER analyses may lead to unrealistic simulations (i.e., too high exposure), reducing the credibility of model-based inferences.
Using brigimadlin, a potent, oral murine double minute 2 homolog-tumor protein 53 antagonist, as a case example, this analysis aimed to:

- Characterize the relationship between safety endpoints and dose modifications.
- Perform dynamic simulations of exposure and safety that account for dose modifications.

Methods

The analysis included the data of brigimadlin administered once every three weeks (Q3W) from Study 1403-0001 (datacut Nov 2021, NCT03449381), a phase Ia/Ib, open label, multicenter, dose-escalation study in patients with advanced or metastatic solid tumors.

A Bayesian model of the probability of dose modification as a function of platelet and neutrophil counts (side effects of this class of drugs) was developed to characterize the dynamic and probabilistic nature of dose decisions. The dose modification model was a composite of one categorical model for the dose decision and one time-to-event (TTE) model for the length of the dose delay. All models were fit using a Bayesian framework with weakly informative priors, and were implemented in Stan using the default no-U-turn sampler (NUTS) with Hamiltonian Monte Carlo method through the brms interface in R [1].

Dose decision model

The dose decision had four categories:

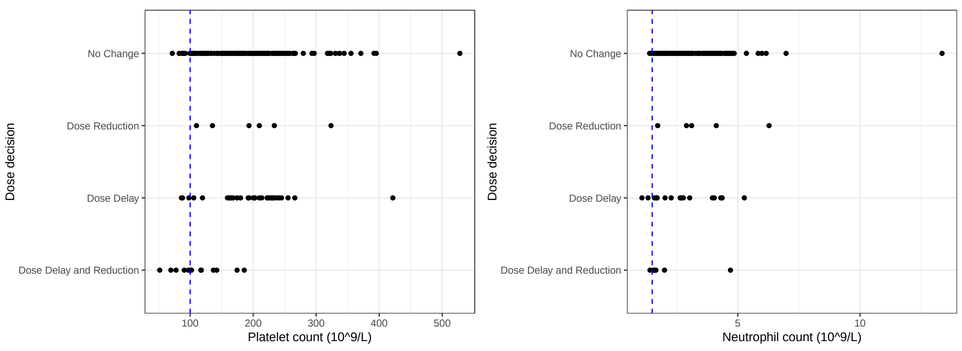
- *No change*: no dose change and no delay.
- *Dose reduction*: a dose reduction without delay.
- *Dose delay*: a delay with no dose change.
- *Dose delay and reduction*: a dose reduction with delay.

A multinomial logistic regression was used to model the categorical outcome 'dose decision', which assumed the probability of dose decision for the next dose was dependent on the platelet and neutrophil counts 21 days after the current dose.

$$\log \frac{Pr(K=k)}{Pr(K=1)} = \alpha_k + \beta_k^{(L)} L + \beta_k^{(N)} N = \eta_k$$

where category 1 is the reference ($\eta_1 = 0$), $K =$ category, $k \in \{2,3,4\}$, $L =$ platelet count, and $N =$ neutrophil count.

Figure 1: Observed dose decision versus platelets and neutrophils, showing physician discretion in dose modifications.



The blue dashed lines are thresholds specified in the study protocol which triggered dose modifications.

Dose delay model

According to the study protocol, any dose administered more than 3 days after the scheduled time (21 days after last dose) was considered as a delay. A TTE model was developed for the length of the dose delay using a Weibull distribution with platelet and neutrophil counts 21 days after dose as predictors.

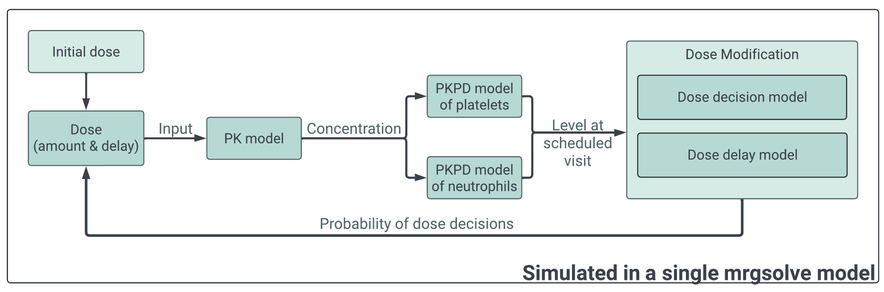
Simulations

The brigimadlin pharmacokinetics (PK) was described using a two-compartment model with first-order absorption and linear elimination. The pharmacokinetic/pharmacodynamic (PKPD) models of platelets and neutrophils were developed using myelosuppression models [2].

A dynamic simulation was conducted using the mrgsolve package in R [3] which simulated the loop of dose to exposure using brigimadlin population PK model, drug exposure to platelets and neutrophils using PKPD models, and platelets and neutrophils to dose decision and dose delay using the dose modification model.

The simulation assumed all subjects started with 45 mg brigimadlin Q3W. Simulated platelet and neutrophil counts 21 days after each dose were monitored and used for decision making for the next dose. The simulation allowed at most two dose reductions from 45 mg to 30 mg and then to 20 mg. If a dose reduction was needed after 20 mg, the treatment discontinued.

Figure 2: Schematic representation of dynamic simulation



Conclusion

A dose modification model was successfully integrated into a dynamic simulation framework accounting for the impact of safety signals on dose. This framework was able to adequately predict the observed safety outcomes and may serve as a basis to support realistic simulations in other oncology drug development programs.

References

[1] Bürkner, P.C. brms: An R Package for Bayesian Multilevel Models Using Stan. *Journal of Statistical Software* **80** (2017):1–28.

[2] Friberg, L.E., Henningsson, A., Maas, H., Nguyen, L. and Karlsson, M.O. Model of chemotherapy-induced myelosuppression with parameter consistency across drugs. *J. Clin. Oncol.* **20** (2002):4713–4721.

[3] Baron, K.T., Gillespie, B., Margossian, C., Pastoor, D., Denney, B., Singh, D., Le Louedec, F. and Waterhouse, T. *mrgsolve: Simulate from ODE-Based Models*. Metrum Research Group (2021).

Acknowledgements

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Results

Dose delays and reductions were estimated to occur more frequently with lower platelet and neutrophil counts (**Figure 3** for platelets, neutrophils not included here); additionally, the delays were longer with lower counts (**Figure 4** for platelets, neutrophils not included here). Simulated patient profiles with dynamic dosing regimens adequately captured the qualitative trajectories of dose decisions, exposure, platelet, and neutrophil counts (**Figure 5**). The simulations including dose modifications were able to predict rates of thrombocytopenia and neutropenia that more closely matched the rates observed in patients than simulations without dose modifications (**Figure 6**). Under the observed inital dose with consideration of dose modifications, the predicted rate of thrombocytopenia $\geq$ Grade 3 was 21.6%, compared to the observed rate of 24.6%, while for neutropenia $\geq$ Grade 3 the predicted rate was 13.8% compared to the observed rate of 17.5%. When not accounting for the dose modifications, the risk of thrombocytipenia $\geq$ Grade 3 was vastly overpredicted (**Figure 6**).

Figure 3: Model predicted probabilities of dose decision versus platelets.

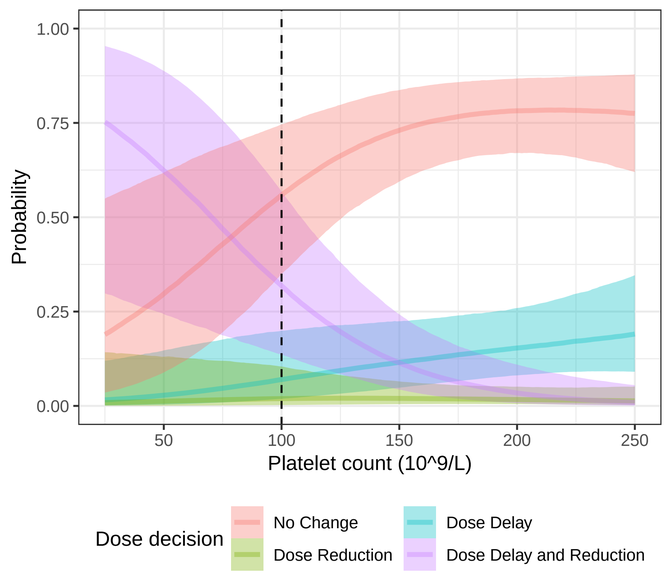
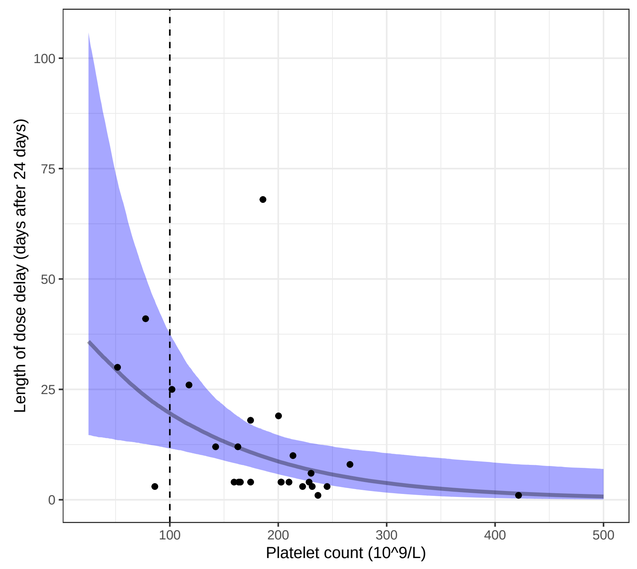
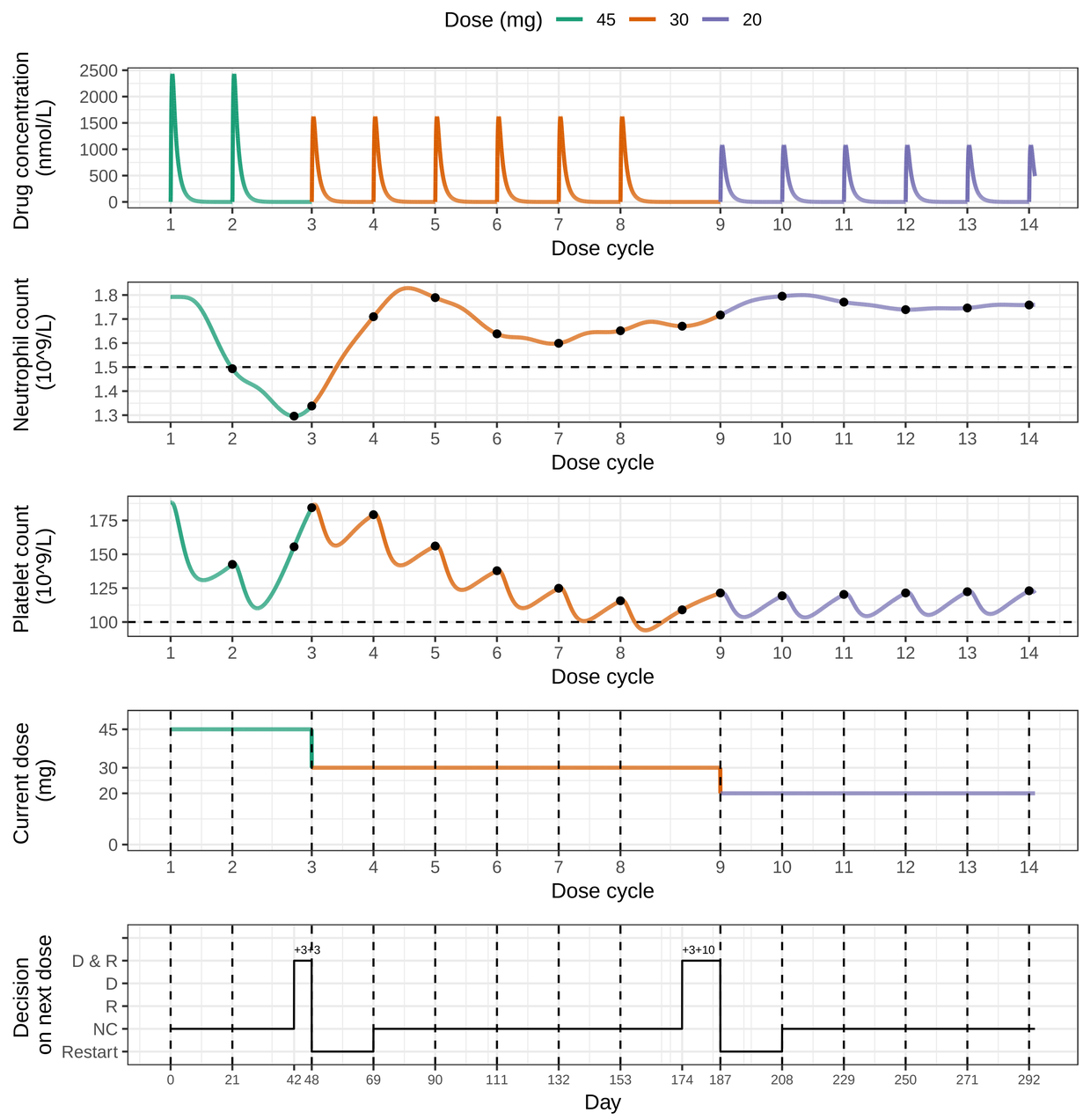


Figure 4: Model predicted length of dose delay versus platelets.



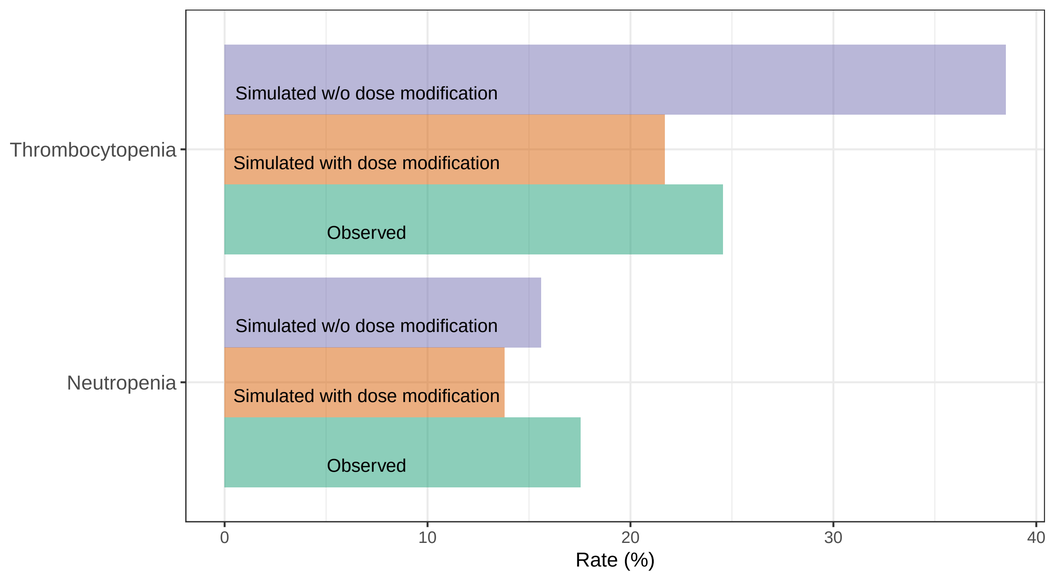
The ribbons represent 90% CIs. The dashed lines are thresholds specified in the study protocol which triggered dose modifications. The black points represent the observed data.

Figure 5: A representative profile of the simulated brigimadlin concentration, neutrophils, platelets, current dose, and dose decision.



The vertical dash lines represent dose events. The horizontal dash lines are thresholds specified in the study protocol which triggered dose modifications. The black points indicate the simulated neutrophils and platelets that were monitored and used for decision making on the next dose. D = dose delay, R = dose reduction, D & R = dose delay and reduction, NC = no change.

Figure 6: Comparison of the simulated and observed rates of thrombocytopenia $\geq$ Grade 3 and neutropenia $\geq$ Grade 3.



The simulations were conducted with the initial brigimadlin dose regimen of 45 mg Q3W.

