Mathematical Optimization of a Thrombopoiesis Quantitative Systems Pharmacology (QSP) Model to Improve Chemotherapy Dosing

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Objectives

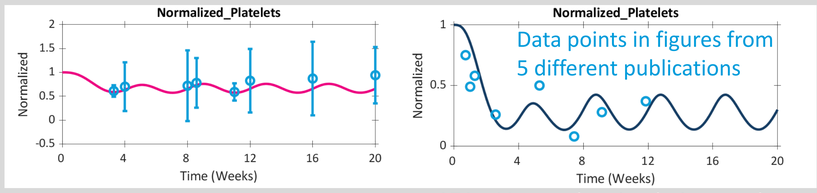
Optimization of thrombopoiesis models

- Thrombocytopenia is a common concern with chemotherapy (CTx)
- Published models of platelet dynamics and regulation of thrombopoiesis use complex mathematical formulations[1,2]
- We developed a QSP model with a minimal structure that reproduces experimental data by:
  1. Improving upon published models' parameters and equations
  2. Evaluating the response to CTx of a virtual patient (VP) with normal platelet levels and a thrombocytopenic VP corresponding to acute myeloid leukemia (AML) patients

Methods

Reducing model complexity

- We researched thrombopoiesis models and identified a recent QSP model[3] as the reference for this work
- We developed a simpler fit-for-purpose thrombopoiesis QSP model using MATLAB® SimBiology® software
- Parameter values were derived from literature or calibrated from thrombopoietin (TPO) and CTx data



AZA simulation results
AZA clinical data

AZA + Venetoclax simulation results
AZA + Venetoclax clinical data

Figure 1. Simulation of AZA ± venetoclax treatment.

Conclusions

Balanced simplicity-to-accuracy ratio

- We present an efficient fit-for-purpose thrombopoiesis QSP model that simulates megakaryopoiesis and platelet dynamics
- Megakaryopoiesis timing and TPO dynamics are accurately represented
- The model has been successfully tested for CTx
- The model can be used for:
  1. Predicting thrombocytopenia risk
  2. Mitigating risk by optimizing protocols
  3. Designing effective concomitant treatment protocols for thrombocytopenia

QSP Model

Thombopoiesis PhysioPD Platform with chemotherapies

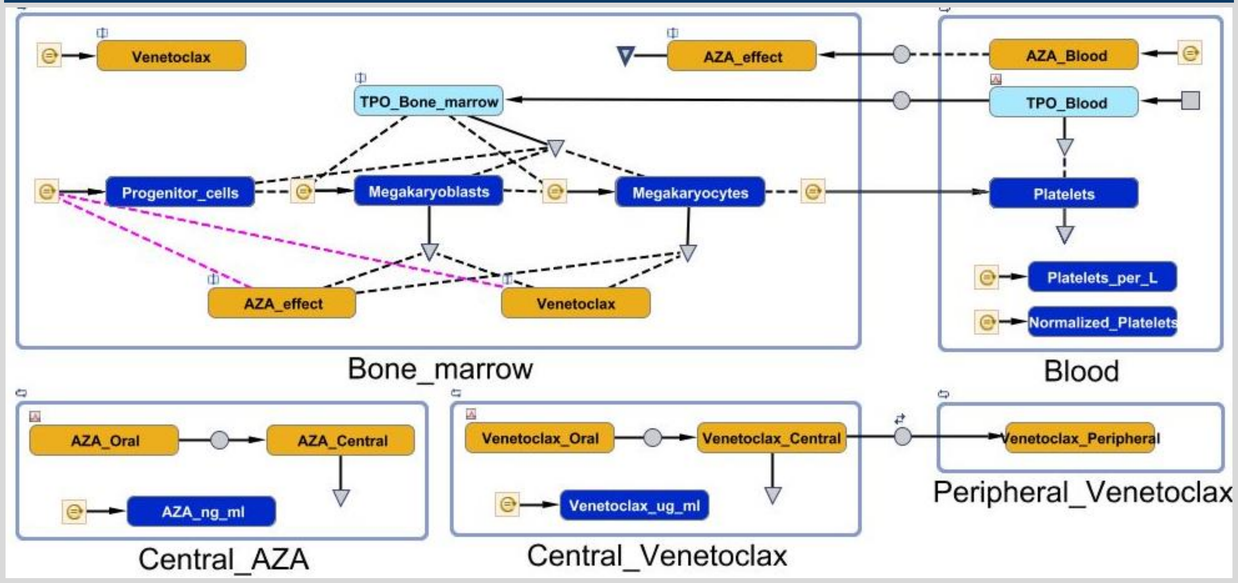


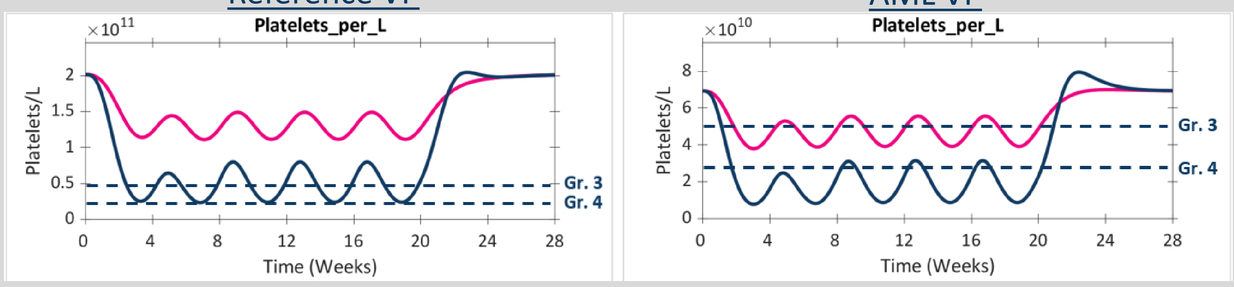
Figure 2. The Thrombopoiesis PhysioMap®, a graphical representation of the model.

- We introduced a more realistic representation of megakaryocyte (MKC) production than the published QSP model[3]: we reduced the number of MKC progenitor species from 28 to 8 and added a constant source of hematopoietic stem cells (HSCs)
- The implementation of TPO dynamics was simplified and its effect on megakaryopoiesis was corrected. The published model did not include effects in all intermediate steps between HSCs proliferation and MKC production
- With these physiologically-based corrections, we were able to capture the complex dynamics of platelet levels
- In addition, we represented CTx using simple expressions and non-regime-dependent parameters, thus allowing for simulating therapy protocols in a wide range of clinical settings, unlike some previous models[4,5]

Results

Platelet and TPO dynamics under CTx are captured

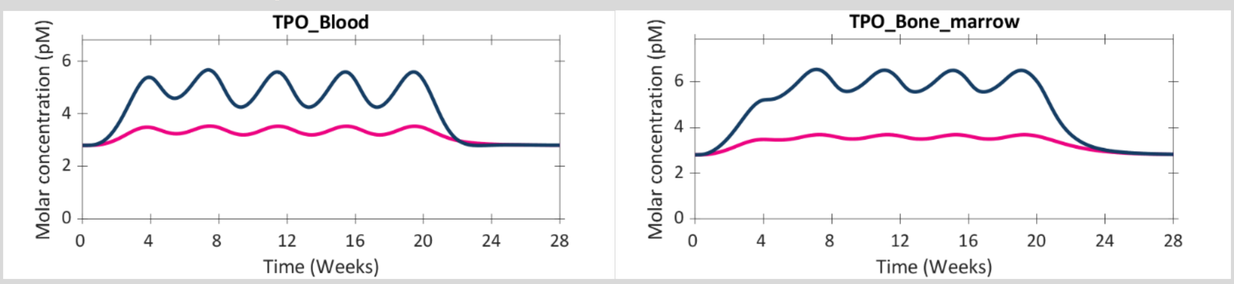
- Simulations of Azacitidine (AZA) monotherapy and AZA + venetoclax combinations in the reference VP matched the reduction in platelet levels measured in various studies
- AZA + venetoclax combination was predicted to induce grade 3 to 4 thrombocytopenia



AZA simulation results
AZA + Venetoclax simulation results

Figure 3. Platelet levels of AZA ± venetoclax dosing in the reference and AML VPs.

- The effect of AZA + venetoclax on TPO was consistent with the doubling of blood TPO levels reported with induction of CTx in AML patients[6]



AZA simulation results
AZA + Venetoclax simulation results

Figure 4. TPO levels of AZA ± venetoclax dosing in the reference and AML VPs.

- Further reductions in the number of bone marrow species fail to reproduce the platelet dynamics, which indicates that an optimal model size has been achieved

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