Evaluation of Potential Low-Dose Regimens of Oral Fixed-Dose Combination of Cytidine Deaminase Inhibitor E7727 with Decitabine (ASTX727-LD) to Minimize Decitabine-Mediated Neutropenia in Low-Risk MDS Subjects Using Systems Pharmacology Modeling

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Abstract #M-009

BACKGROUND AND INTRODUCTION

- Decitabine (DAC) is a well characterized hypomethylating agent (HMA), which is incorporated into DNA during the S-phase of cell cycle, inhibits methylation of antitumor genes and induces G2/M arrest.
- DAC is approved for treatment of int-high risk Myelodysplastic Syndromes (MDS), a disease characterized by ineffective hematopoiesis and dysplastic cells in bone marrow
- DAC is rapidly degraded by cytidine deaminase (CDA), resulting in poor oral DAC bioavailability and systemic exposures.
- ASTX727 is being investigated as an oral, fixed dose combination (FDC) of a novel potent oral CDA inhibitor, E7727, with oral DAC for the treatment of patients with int.-high-risk MDS or Chronic Myelomonocytic Leukemia (CMML).
- Low doses of oral DAC co-administered with E7727 have been shown to produce exposures similar to intravenous (IV) DAC with acceptable inter-patient variability.
- Low risk MDS (LR-MDS) patients present with <5% of leukemic blasts in bone marrow and anemia or cytopenia(s).
- Treatment with DAC causes side effects such as neutropenia and/or thrombocytopenia
- The objective of this work was to use systems pharmacology modeling to describe the effect of DAC on neutrophils and simulate regimens to minimize myelosuppression.

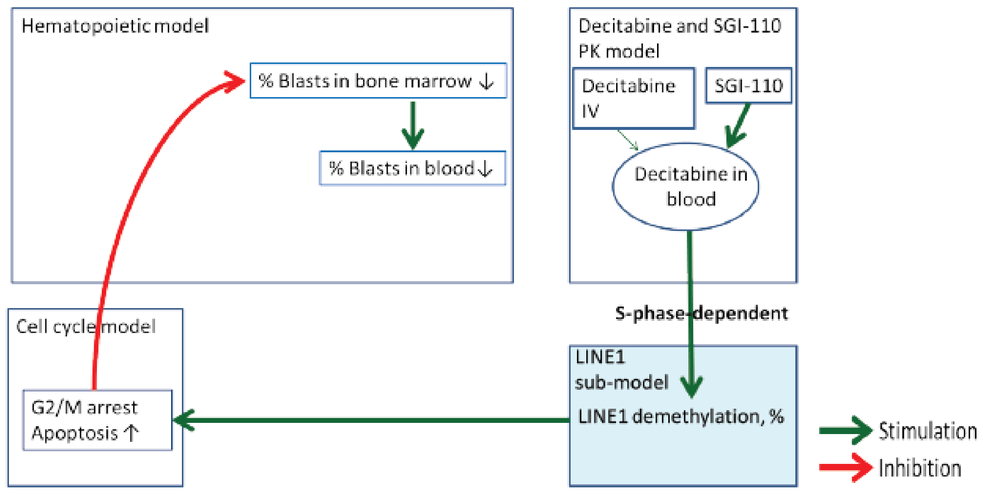
METHODS

A quantitative systems pharmacology (QSP) model was previously developed describing myeloblasts cell cycle; leukemic blasts, neutrophils and platelets in physiological compartments (bone marrow and blood); PK of DAC after IV infusion, after dosing with subcutaneous guadecitabine (SGI-110, a dinucleotide of DAC linked to deoxyguanosine) and oral ASTX727 [1, 2]; PD marker of LINE-1 demethylation changes following treatment with HMAs; and effects of DAC on leukemic cells, neutrophils and platelets (Figure 1). Model parameters were identified against in vitro and clinical data.

The effect of DAC on neutrophils was described using two additional variables (Figure 2) Tox1 and Tox2. Tox1 depends on DAC levels in plasma. Parameters were calibrated against clinical data on neutrophil count during treatment of AML patients with guadecitabine (unpublished data, Figure 3).

The EC50 of DAC effect on neutrophils was fixed based on published in vitro data. The model was validated against clinical data on blast dynamics in blood and bone marrow of relapsed/refractory AML/MDS patients that were responders to treatment with guadecitabine.

Figure 1. Block-scheme of Systems Pharmacology Model of Acute Myeloid Leukemia



Key differential equations for the model

$\frac{dNph\_bld}{dt} = \frac{V\_maturation\_nph - V\_degel\_nph}{BLD}$

Concentration of neutrophils in blood, BLD – volume of compartment "Blood". Concentration of platelets and RBC are described in the model by the same approach. Direct effect of decitabine on neutrophil counts in blood (DAC-induced neutropenia) is described by Michaelis-Menten-like equation with a dependence on additional variable "Tox2" (Figure 2).

$\frac{dBlast\_G1}{dt} = \frac{V\_maturation\_blast + V\_g0\_to\_g1 - V\_g1\_to\_s - 2*V\_g2m\_to\_g1 - V\_g1\_to\_apo - V\_bm\_to\_bld\_g1}{BM}$

Concentration of leukemic blasts in G1 phase of cell cycle in bone marrow, BM – volume of compartment "Bone marrow"

$\frac{dBlast\_G0}{dt} = \frac{-V\_g0\_to\_g1 - V\_bm\_to\_bld\_g0}{BM}$

Leukemic blasts in G0 phase of cell cycle in bone marrow

$\frac{dBlast\_S}{dt} = \frac{-V\_g1\_to\_s - V\_s\_to\_g2m - V\_s\_to\_g2mh}{BM}$

Leukemic blasts in S phase of cell cycle in bone marrow

$\frac{dBlast\_G2M}{dt} = \frac{V\_s\_to\_g2m - V\_g2m\_to\_g1}{BM}$

Leukemic blasts in G2M phase of cell cycle in bone marrow

$\frac{dBlast\_Apo}{dt} = \frac{V\_g1\_to\_apo - V\_apo\_to\_death}{BM}$

Leukemic blasts in apoptosis in bone marrow

$\frac{dBlast\_Death}{dt} = \frac{V\_apo\_to\_death + V\_apoh\_to\_death}{BM}$

Leukemic blasts in "death" condition in bone marrow

$\frac{dBlast\_bld}{dt} = \frac{V\_apo\_to\_death + V\_apoh\_to\_death}{BM}$

Concentration of leukemic blast in blood, BLD – volume of compartment "Blood"

$\frac{dBlast\_G2Mh}{dt} = \frac{V\_s\_to\_g2mh + V\_g2mh\_to\_apoh}{BM}$

Leukemic blasts in G2M phase after DNA hypomethylation induced by DAC

$\frac{dBlast\_Apoh}{dt} = \frac{V\_g2mh\_to\_apoh - V\_apoh\_to\_death}{BM}$

Leukemic blasts in apoptosis after G2M phase arrest in of cell cycle

RESULTS

- The model was successfully calibrated and validated against various types of data, and successfully reproduces clinical data on neutrophil counts following treatment with guadecitabine (Figure 3)
- In accordance with [3], the model shows that DAC-induced neutropenia is not the result of gene demethylation or DAC incorporation into DNA, but has a complex mechanism that depends on DAC levels in plasma
- Simulations with several regimens using low doses of DAC for ASTX727 administration were performed. The model predicts that neutrophil levels depend on the dose and frequency of ASTX727 administration (Figure 4)
- Model suggests that the least toxic ASTX727-LD regimen among those simulated was the 5mg DAC / 100 mg E7727 Daily X5 for 2 weeks, repeated every 28-day cycle (green curve, Figure 4)
- ASTX727-LD Regimens of 10/100 mg Daily X3 for 3 weeks; and 20/100 mg Daily X3 for 2 weeks had a similar effect on neutrophil dynamics., whereas the effect on leukemic blasts (not shown) was better with the 10/100 mg Daily X3 for 3 weeks regimen

Figure 2. Scheme of DAC-induced neutropenia description in the model

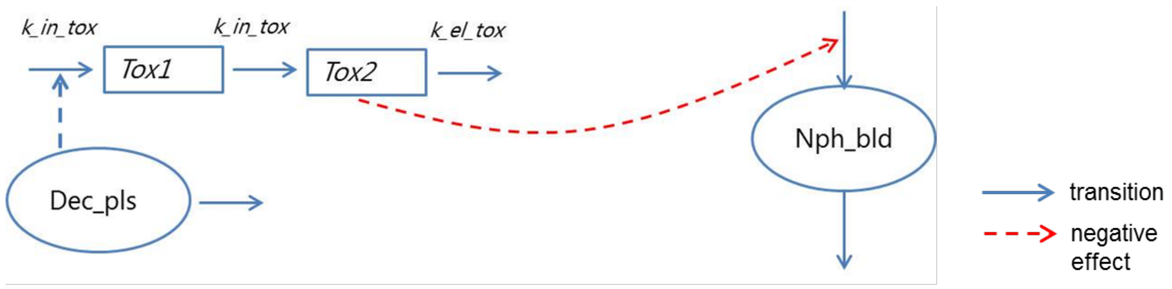


Figure 3. Neutrophil dynamics after guadecitabine treatment of AML patients (responders) using Daily X5 every 28-days. Fitting results, observed vs predicted.

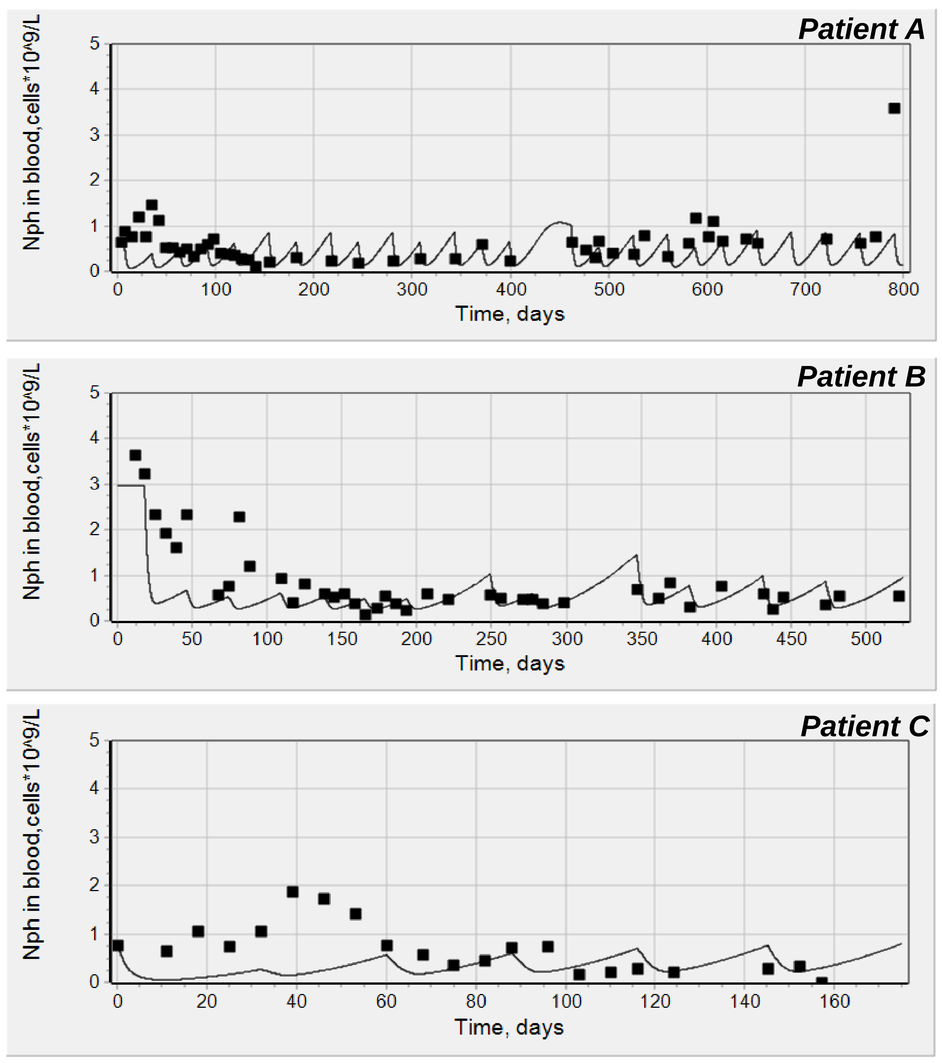
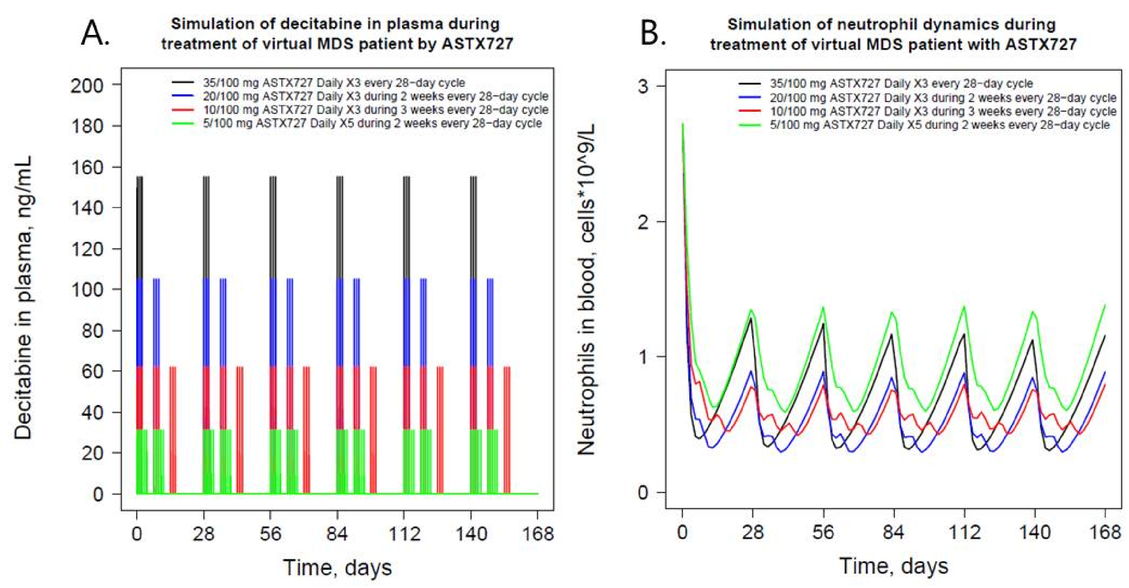


Figure 4. Simulation of DAC in plasma (A) and neutrophil dynamics (B) during treatment of virtual MDS patients with varying regimens of ASTX727



SUMMARY/CONCLUSIONS

A previously developed systems pharmacology model for AML progression and treatment was updated and adequately describes available data on neutrophil dynamics after treatment with guadecitabine.

Model allows simulation of lower doses of varying regimens for optimization of treatment with ASTX727 to minimize DAC-mediated adverse effects such as neutropenia and potentially maximize efficacy.

The model suggests that the optimal regimen of ASTX727 that induces minimal changes in neutrophil counts and with potential maximal effect on leukemic blasts in BM consists of low dose of 5 mg DAC with 100 mg E7727, dosed Daily X5 for 2 weeks of every 28 days.

The model data and outputs need to be confirmed in prospective clinical trials of low dose oral DAC with E7727.

REFERENCES

1. 2015 ASCPT: Systems Pharmacology Modeling of Hypomethylating agents Decitabine and SGI-110 for Evaluation of AML treatment by targeting the S-phase with prolonged Pharmacokinetic exposures, A. Oganesian, O. Demin Jr. , A. Nikitich, O. Demin and M. Azab.
2. 2017 ASCPT: Development of a Semi-Mechanistic PK/PD Model of an Oral Fixed Dose Combination (FDC) of Cytidine Deaminase Inhibitor E7727 with Decitabine (ASTX727) in Subjects with Myelodysplastic Syndromes, Eric G. Burroughs, Aram Oganesian, Xiaoping Zhang, and Frank Hoke.
3. Leukemia. 2012 February ; 26(2): 244–254.

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