Systems Pharmacology Modeling of Hypomethylating agents Decitabine and SGI-110 for Evaluation of AML treatment by targeting the S-phase with prolonged Pharmacokinetic exposures

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BACKGROUND

Acute myeloid leukemia (AML) is a tumor associated with myeloid line of blood cells, characterized by the abnormal rapid proliferation of white blood cells in the bone marrow. The most common approach for AML treatment is the reduction of abnormal cell proliferation rate which can be achieved by targeting the key stages of the cell cycle.

Decitabine is a well characterized hypomethylating agent (HMA), which is incorporated into DNA during the S-phase of cell cycle, inhibits methylation of tumor genes and induces G2/M arrest. However, it has a very short half-life (15-35 min) after IV infusion due to rapid degradation by cytidine deaminase. SGI-110, a 2nd generation HMA was designed to increase the in vivo exposure/potential efficacy of its active metabolite decitabine. The aim of the effort was to explore how changes in exposure window of decitabine affect DNA demethylation and tumor cell proliferation in AML patients.

MATERIALS and METHOD

A systems pharmacology model was developed describing myeloblasts cell cycle. PK of decitabine after IV infusion and after dosing with SQ SGI-110; LINE-1 demethylation changes following treatment and progression of AML. The model is a system of differential equations characterizing myeloblasts transition between cell cycle phases and proliferation of healthy neutrophils. Parameters of the model were calculated on the basis of the literature data or fitted against available and published experimental data. 95% confidential intervals were calculated for fitted parameters.

RESULTS

The model satisfactorily reproduces following data:

- In vitro data from experiments with myeloblast cell lines showing proliferation and distribution between cell cycle phases with or without decitabine treatment.
- PK of decitabine after 1 hr IV infusion at 20 mg/m² after IV infusion due to rapid degradation by cytidine deaminase.
- SGI-110, a 2nd generation HMA was designed to increase the in vivo exposure/potential efficacy of its active metabolite decitabine.
- Model satisfactorily predicts bone marrow and peripheral blast dynamics in responders to SGI-110.

CONCLUSIONS

- Prolonged exposure window of active metabolite of SGI-110, decitabine, leads to a more pronounced effect on LINE-1 demethylation.
- Simulations in virtual AML patients showed that SGI-110 performed better than IV decitabine in affecting proliferation of myeloblasts in bone marrow and peripheral blood.
- Model successfully predicts blast dynamics in responders to SGI-110.