Identifying Optimal Panobinostat Treatment Regimens Utilizing Reverse-Engineered Concentration-Time Curves

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Introduction

Multiple Myeloma (MM) is a blood plasma cancer characterized by a high recurrence rate. The American Cancer Society projects ~32,000 Americans will be diagnosed with MM in 2020. The Ex vivo Mathematical Myeloma Advisor (EMMA) is a mathematical model used to personalize MM treatment. A patient’s cancerous blood plasma cells are co-cultured with chemotherapies in micro-well plates, and plates are imaged to produce cell viability graphs. For each chemotherapy tested, EMMA is fit to its cell viability graph, and it parameterizes a mathematical model of patient sensitivity.

To more accurately predict the effect a chemotherapy will have in a patient, EMMA must interface the patient’s sensitivity model to the chemotherapy, with a treatment scheduling curve of that same chemotherapy. This treatment scheduling curve numerically depicts the concentration of drug that will be present in the patient’s bloodstream over their entire treatment period. Treatment scheduling curves of a drug are produced from concentration-time curves of the drug.

Since only certain key metrics of concentration-time curves are released to the public (e.g. AUC_t, C_max, and t_max) and not the curves themselves, optimal EMMA functionality is hindered. To resolve this, I formulated a novel mathematical model to reconstruct the concentration time curves of Panobinostat (PAN), a standard MM chemo-therapeutic, using publicly reported metrics. I reconstructed the standard PAN scheduling curve and nine alternative PAN scheduling curves which varied in frequency versus intensity of treatment. I interfaced each PAN scheduling curve with 243 logged EMMA models of patient PAN sensitivity to investigate if introducing alternative PAN schedules impacted patient Best Response predictions. Best Response is an EMMA-predicted measure of the largest % reduction in tumor volume a patient will experience over the course of their treatment period.

Research Objectives

1. Formulate a novel mathematical model to reconstruct Panobinostat (PAN) Concentration-Time Curves from key reported metrics
2. Construct Traditional & Alternative PAN treatment scheduling curves to investigate impact on EMMA Best Response predictions

Alternative Treatment Schedules

The immediate application this pharmacokinetic model is that Panobinostat treatment scheduling can now be optimized on a per-patient basis for partial responders. The optimal treatment schedule, which is generally H_A or F, is the one which produces the largest EMMA Best Response prediction.

The broader application of this pharmacokinetic model is that it can be fit to reconstruct the concentration time curves of any orally administered chemotherapy, thereby allowing treatment scheduling for that chemotherapy to be meaningfully optimized for partial responders.

My research is currently being used at the Moffitt Cancer Center to advise treatment scheduling for partial responders to Panobinostat.

References


Future Research

1. Complete Response Patients cohort
2. Future research lies in optimizing the treatment scheduling of the complete responders cohort. Optimal schedules for this cohort would reduce the amount of Panobinostat administered, while maintaining high efficacy (>50% Best Response reading).

Application & Implication

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