Systems Pharmacology Modeling for Optimization of Target Therapy for Melanoma

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Objectives: To develop a systems pharmacology model of melanoma progression and treatment with approved targeted therapies (vemurafenib, dabrafenib, trametinib) and to optimize dosages and regimens of monotherapies and combination therapies for different types of patients.

Methods: The model is a system of ordinary differential equations describing tumor growth in melanoma patients, vemurafenib, dabrafenib and trametinib pharmacokinetics (PK) and inhibitory effect on melanoma cells’ proliferation. PBPK approach was used to describe the concentration of compounds at site of action in vivo. The effect of compounds were calibrated on the basis of in vitro data on culturing of melanoma cancer cells with different concentrations of vemurafenib, dabrafenib and trametinib. PK parameters were taken from FDA clinical pharmacology reviews of these drugs. Parameters of tumor growth in vivo in melanoma patients were identified on the basis of clinical data on tumor growth without treatment (tumor growth before surgery, time to metastasis, clinical cases). Clinical data on changes in tumor volume during treatment of melanoma patients with monotherapies or combination therapies of vemurafenib, dabrafenib and trametinib was used for model validation.

Results: Model is able to describe the clinical data on tumor volume changes during treatment with vemurafenib, dabrafenib and trametinib (Figure 1). Different types of virtual patients (VP) were described in the model including VP with different rate of tumor growth and response to particular compound (sensitive/resistant). Model shows that dose reduction in 2-4 times in comparison with recommended dose for each drug does not lead to a significant change of therapy efficiency. Alterations of approved regimens also have no effect on the results of monotherapy. Vemurafenib/trametinib (has not been investigated previously) shows similar efficacy as combination of dabrafenib and trametinib across all types of virtual patients.

Conclusions: Developed model satisfactorily reproduces experimental data for various types of patients melanoma. Model could be used as a tool for optimization of new target therapies for melanoma treatment.

Figure 1. Model validation against clinical data on tumor volume changes during treatment of individual melanoma patients with: (A) 960 mg BID vemurafenib; (B) 150 mg BID dabrafenib; (C) 2 mg QD trametinib.