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IL-21 immunotherapy in solid cancers: Therapeutic insights from a preclinically validated mathematical pharmacokinetic and pharmacodynamic model

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Background: The new immunomodulatory protein interleukin 21 (IL-21) promotes potent antitumor responses in solid cancers, in both preclinical and clinical studies. Yet due to diverse effects of IL-21 on the immune system and its potential toxicity, the conditions for optimal therapy by this cytokine remain elusive. A previously described mathematical model for the tissue-localized "*in situ*" effects of IL-21 immunotherapy in solid cancers accurately retrieved the effects of IL-21 gene-therapy in mice, and served a basis for initial development of efficacious therapeutic regimens that consider drug-associated efficacy and toxicity. To suggest improved treatment strategies for IL-21 that are clinically relevant, we aimed at advancing the model into a full systemic murine pharmacokinetic/pharmacodynamic (PK/PD) model, and to validate its accuracy in the preclinical setting. **Methods:** The *in situ* PD model was integrated with an 8-compartment PK model considering non-intravenous or intravenous routes of drug administration. PK model parameters were estimated using data from wild-type mice treated with standard IL-21 injections. PD model parameters were set as evaluated in the gene-therapy treated mice, and baseline tumor growth parameters were newly estimated using data from untreated melanoma (B16) and renal cell carcinoma (RenCa)-bearing mice. The parameter describing the ratio between drug concentrations in plasma and in tissue was evaluated within a general range, and also within a narrower range determined according to murine IL-21 biodistribution data for each tumor type and administration route. The model was simulated under various preclinical treatment schedules, and its predictions were compared to experimental results using curve-fitting and statistical methodology. Simulation of a wider range of putative treatment regimens was also performed. **Results:** The PK/PD model was validated by its retrieval of B16 and RenCa tumor growth curves in wild-type and immunodeficient mice under different IL-21 regimens, with negligible errors. Most model parameters were independent of tumor type and treatment strategy, confirming the model's generality and robustness. The parameter for drug concentrations ratio showed low sensitivity, satisfying model validation for all values within its estimated narrow indication-specific and administration route-specific range. The model predicts that efficient tumor reduction can be achieved by regimens applying non-intravenous doses between 0.2-2 mg/kg at inter-dosing intervals between 1-3 days. Our analysis also demonstrates the importance of early treatment and suggests the use of non-uniform dosing and timing throughout therapy, as well as further regimen fractionation. **Conclusions:** Our model for the effect of IL-21 on tumor growth has been validated with murine data in a therapeutic setting, and thereby demonstrated robustness of the model predictions. By adapting plasma/tissue IL-21 concentration ratios for each

tumor type and drug administration route, and by considering different baseline dynamics of each tumor, the model can support various solid cancer indications, therapeutic strategies and populations with different tumor load. The model suggests that regimens with significantly lower dose intensity, and therefore less drug-associated toxicity, can be as efficacious as those previously tested, which could potentially also be the situation in the clinical setting.

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