Maximum Tolerated Dose or Low-Dose Metronomic Regimen: Implication by A Cellular Pharmacodynamics Model Based on in vitro Cytotoxic Data

Hua He1,2, Yanguang Cao1*

1DPET, School of Pharmacy, University of North Carolina at Chapel Hill, NC, USA; 2China Pharmaceutical University, Nanjing, China.

Objectives: The dosing regimen of traditional maximum tolerated dose (MTD: high dose, low frequent) is often challenged by low-dose metronomic (LDM: low dose, high frequent) dosing in many chemotherapies. However, it remains unclear which types of chemotherapies would significantly benefit from LDM dosing. The aim of the present study was to develop a cellular pharmacodynamics (PD) model that analyzed in vitro cytotoxic data to select the favorable dosing regimen between MTD and LDM.

Methods: The developed PD model divided cancer cells into two subpopulations that were assumed susceptible to either concentration- or time-dependent cytotoxicity. The cellular PD model was taken to analyze various types of in vitro cytotoxic data. The model was further used to simulate tumor suppressive effects of paclitaxel at two commonly dosing regimens. MTD and continuous constant infusion (an extreme LDM) were extensively compared based on the developed model to explore critical factors that largely determine the optimal dosing regimen between MTD and LDM.

Results: The developed cellular PD model adequately captured various patterns of concentration-tumor survival curves obtained in in vitro toxicity assay. The ratio of drug concentrations ($C_a$) to cytotoxic sensitivity ($KC_{50}$) and the fraction of time-dependent subpopulation ($f_u$) were found two critical factors. A Cellular PD model Predicted Dosing System (CPPDS) was then developed, where four classes of chemotherapies were defined: Class I (high $C_a/KC_{50}$, low $f_u$), Class II (high $C_a/KC_{50}$, high $f_u$), Class III (low $C_a/KC_{50}$, high $f_u$), and Class IV (low $C_a/KC_{50}$, low $f_u$). Our results indicated that only chemotherapies in Class IV favor MTD with all other Classes in preference of LDM, among which Class I highly benefit from LDM.

Conclusions: The developed cellular PD model and CPPDS presented a simple and innovative approach to guide the selection of optimal dosing regimen in chemotherapy.

Figure 1. Simulation of the antitumor effect of paclitaxel at different clinical dosing schedules.