B-cells kinetics after acute depletion following brain irradiation in preclinical context: a semi-mechanistic modeling and simulation approach

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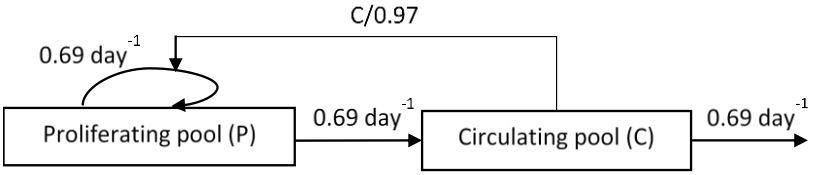
Abstract

Recent publications point out the importance of B-cells in regulating tumor control. B-cells are among the most radiosensitive cells and their recovery could take months to years after radiotherapy (RT). We developed a mathematical model for B-cell recovery following brain RT in rodents that is able to predict the long-term effect of radiation on B-cell population.

Longitudinal data of B-cell concentration after brain irradiation with X-ray in mice were obtained. C57Bl/6 mice (n=40) were irradiated under anesthesia for whole-brain or hemispheric irradiation at 1 or 2 Gy/min twice a day on 2 consecutive days until 20 Gy. Blood samples were withdrawn at day 3, 7, 14 and 28 after irradiation (XRAd 225Cx). Relative concentration over non-irradiated group at each time point was calculated. Radiation covariates were dose rate (1 or 2 Gy/min) and spatial coverage (whole-brain or left hemisphere).

Exploratory data analysis was performed and showed a similar trend as Friberg's model used in myelosuppression, thus this model was applied as a general model structure. Model fitting with least square method was applied by Levenberg-Marquardt algorithm. First, optimal model structure was selected based on lowest mean square error. Second, parameters were estimated. Final model was used to simulate and predict B-cell recovery following irradiation. Individual-based modeling (IBM) was then applied in assuming inter-individual heterogenous baseline. Visual predicted check was used for IBM qualification. Anova and correlation analysis was used to search for the relationship between individual baseline predicted by the model and covariates involved in B-cells regulation after brain irradiation. Modeling, simulation and data analysis were applied in R.

200 measurements of B-cell concentration after irradiation in 40 mice were used for model construction. A two-compartment model was selected as optimal model structure. Parameter estimation was statistically significant ($p<0.001$). The predicted baseline value was approximate 1, thus B-cell level nearly reaches its initial level after completion of irradiation.



By simulation, kinetics of B-cells described by the model fitted the original data curve quite well. A steady state was reached about 15 days after RT. IBM resulted in a model well fit with observations. Individual predicted baseline was well correlated with initial loss after RT after low radiation rate (1 Gy/min).

This study provides a potential semi-mechanistic modelling approach for studying the effect of irradiation on B-cells. The model was consistent with the theory of B-cells homeostasis and population cells kinetics in the body. This modeling approach will be assessed in a comparative study of different radiation beam types and extrapolated for B-cell surveillance following RT in clinical context.

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