Glioblastoma cell variability and circadian rhythms control temozolomide efficacy: from cellular pharmacokinetics-pharmacodynamics to heterogeneous cancer cell population models

Annabelle BALLESTA, Unité Inserm 900 - Saint-Cloud & Paris
Hugo MARTIN, Unité Inserm 900 - Saint-Cloud & Paris

Glioblastoma (GBM) is the most common and aggressive primary brain tumor in adults, and is currently associated with a dismal prognosis despite intensive treatments combining surgery, radiotherapy and temozolomide-based chemotherapy. Clinical trials over the last two decades testing various multi-agent pharmacotherapies have failed demonstrating any significant patient survival improvement so far. Chronotherapy, that consists in administering antitumor drug according to the patient's 24h-rhythms is considered as a promising therapeutic approach to improve treatment tolerability and efficacy. Recent clinical and preclinical studies have highlighted the dependency of temozolomide (TMZ) efficacy on administration timing [3, 2]. In order to obtain quantitative predictions on the mechanisms underlying temozolomide chronoefficacy, we designed a systems pharmacology model at the cell population level as follows. A simplified ODE-based model of TMZ pharmacokinetics-pharmacodynamics (PK-PD) was connected to a model representing the cancer cell population dynamics though a PDE structured in the amount of DNA damage in a cell and sensitivity to damage. The PK part of the ODE model was fully designed and calibrated to data [1], whereas the remaining elements of this combined model were inferred from cell culture circadian datasets ([3] and unpublished data). To properly fit all datasets, we had to include in the model an inter-cell variability accounting for different rates of DNA damage formation for a given drug dose. This addition allowed a successful model calibration, in contrast to the model in which population heterogeneity came solely from the initial damage distribution, prior any drug exposure.

Références

[1] A Ballesta et al. « Multiscale Design of Cell-Type–Specific Pharmacokinetic/Pharmacodynamic Models for Personalized Medicine : Application to Temozolomide in Brain Tumors ». In : *CPT Pharmacometrics Syst. Pharmacol.* 3.4 (avr. 2014), e112.

[2] Anna R Damato et al. « Temozolomide chronotherapy in patients with glioblastoma : a retrospective single-institute study ». In : *Neuro-Oncology Advances* 3.1 (jan. 2021).

[3] Emily A. Slat et al. « Cell-intrinsic, Bmal1-dependent Circadian Regulation of Temozolomide Sensitivity in Glioblastoma ». In : *Journal of Biological Rhythms* 32.2 (mar. 2017), p. 121-129.

Contact : hugo.martin@inserm.fr