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

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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 multiagent 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[1], whereas the remaining elements of this combined model were inferred from cell culture circadian datasets ([3] and unpublished data).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

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