Temozolomide cellular Pharmacokinetic/ Pharmacodynamic Models in the context of Brain Tumours

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Abstract

Glioblastoma multiforme (GBM) is the most frequent and aggressive type of primary brain tumours in adults. Despite very intensive treatments including maximal safe neurosurgery, radiation therapy and chemotherapy, the prognosis of GBM patients remains poor with a median overall survival below 18 months. Temozolomide (TMZ)-based chemotherapy is the most com- mon pharmacological treatment in patients with diagnosed GBM. Even if TMZ administration improves patient overall survival, prognosis remains poor and no major therapeutic advance has been accomplished within the past 10 years. This can be related to a lack of knowledge in how the tumour evolves and ultimately escape drug activity, especially in a context of large inter-patient variability.

New systems pharmacology approaches combining experimental and mathematical expertise provide interesting perspectives towards the design of safe and efficient TMZ-based therapies against GBM. The present study aims to do so through the conception of a model of TMZ pharmacokinetics-pharmacodynamics (PK-PD) and of key regulatory networks, capable of reproducing the intracellular events from TMZ exposure to cell rescue or apoptosis. TMZ is a methylating agent that creates lesions on the DNA after a two-step activation process. Four types of DNA adducts are formed upon drug exposure, which are handled either by O6- methylguanine-DNA methyltransferase (MGMT) or by the base excision repair (BER) system. If DNA repair is unsuccessful, DNA single- or double-strand breaks are created, which triggers Homologous Recombination (HR), ATR/Chk1 and p53 activation, cell cycle arrest and possibly apoptosis.

We designed a model, based on ordinary differential equations, that recapitulates these intra- cellular events. Then, model calibration consisted in a modified least square approach ensuring data best-fit satisfied biologically-sound constraints, the numerical minimization problem being performed by the Covariance Matrix Evolutionary Strategy (CMAES) algorithm. The model was able to reproduce multi-type datasets of several independent studies mostly performed in either the U87 or LN229 glioblastoma cell lines. These datasets included

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longitudinal and dose-dependent studies of TMZ cellular PK, DNA adduct formation, ATR, Chk1 and p53 phosphorylation, and cell death. This calibrated PK-PD model is currently being used as a powerful tool to investigate new therapeutic targets. Drug combinations involving TMZ and one to three targeted therapies are explored, among which clinically available inhibitors of ATR (e.g. Berzosertibe), PARP (e.g. olaparib) or Cyclin Dependent Kinase4/6 (e.g. palbociclib). The next step will imply a partial re-calibration of the model with multi-omics datasets available for GBM patient-derived cell lines or GBM patient samples, towards a mechanism-based personalization of GMB treatment.