Glioblastoma treatment with temozolamide and DNA damage-repair inhibitors: an *in silico* clinical trial

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The average life expectancy of patients diagnosed with glioblastomas is 14 months with treatment. Standard treatment includes the chemotherapeutic drug temozolomide, that works by inducing DNA methylation. However, the BER and MGMT repair pathways efficiently repair the damage caused by this drug, reducing the efficacy of treatment. It has been hypothesized that inhibiting these repair pathways may lead to overcoming chemotherapy resistance. In this talk, I will present a novel mathematical model that captures the effect of chemotherapy on brain cancer cells, and includes detailed mechanisms of DNA damage and repair. The model is extensively parametrized and carefully validated using a wide array of available experimental data. Issues of parameter identifiability are also investigated. A global sensitivity analysis is performed to reveal those parameters most critical in the emergence of chemotherapy resistance. The calibrated model is then applied to predict treatment strategies that are optimized with respect to specific cancer cell phenotypes. A virtual cohort of glioblastoma patients – each with a heterogeneous tumor – is created, and a genetic algorithm employed to identify optimal treatment strategies. Our results suggest that patients can be broadly classified into 4 types in terms of these dosage schedules, based on the overall phenotypes of their tumors. Thus, resistance to chemotherapy can be mitigated to a certain extent by using novel dosage schedules, and combining standard treatment with cell-repair enzyme inhibitors.