Modelling and simulation approaches to predict brain and CSF distribution of oncology compounds in glioblastoma multiforme (GBM) or brain metastatic (BM) patients

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Objectives: Treating brain tumours, especially in glioblastoma multiforme or brain metastatic patients, is challenging due to poor understanding of disease progression and the role of the blood-brain-barrier (BBB) in limiting exposure of drugs to site of action. It is difficult to obtain in vivo brain/cerebrospinal fluid (CSF) samples from these patients. Physiologically based pharmacokinetic (PBPK) modelling tools were used to maximize the application of data generated from the in vitro assay systems to predict human CSF or brain exposure with eight tyrosine kinase inhibitors (TKI).

Methods: Apparent permeability and efflux ratios for of eight TKI were determined in Caco-2 and double-transfected MDCK cells overexpressing efflux transporters of interest (e.g. P-gp, BCRP etc). A whole-body PBPK model with a 4-compartment permeability-limited brain model was developed and the model fitting was verified using observed plasma, brain, and CSF data in patients with brain tumors. Simulations were performed to examine the impact of BBB passive permeability, uptake/efflux transporter clearance and brain unbound drug fraction (fu,br) on brain penetration of TKI.

Results: Two TKI, AZD3759 and ibrutinib, were highly permeable compounds but were not a substrate for P-gp or BCRP. Osimertinib, erlotinib, gefitinib, crizotinib, olaparib, and lapatinib were substrates for either P-gp or BCRP or both. The steady-state mean plasma values predicted were within a range of 0.67 and 1.5-fold of the observed data, while CSF or brain tumor concentration predictions fell within 0.5 to 2-fold range.

Conclusion: A brain-oriented, in vitro-in vivo extrapolation-PBPK model appears to be useful to quantify the CNS exposure and predict the pharmacology of anti-tumour targeted TKI drugs under various scenarios.