Performance Verification of V17 Sim-Cancer Population in Simcyp

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Background

Oncology is an important area of pharmaceutical research. PBPK modelling can aid in oncology drug development when physiological and demographic differences in cancer patients compared to healthy volunteers are appropriately considered. For Simcyp V17 a Sim-Cancer population has been developed, taking into account differences in patient demographics and physiology. It has been debated in recent literature whether CYP abundance changes in cancer [1,2]. For the Sim-Cancer population no changes were made to CYP abundance. Performance verification of the population has been performed using a variety of probe CYP and transporter substrates.

Methods

PK studies were collated from the literature for Simcyp Probe Substrates in cancer patients. Simulations were performed using matched trial designs with the Sim-Cancer population and the Simcyp compound files (without alteration) in Simcyp V17. Predicted PK parameters were compared to the reported values. Predicted AUCs are calculated for the same duration as the observed studies. PK studies in healthy volunteers using the same drugs and dosing regimens to the cancer studies were also collated where possible. Simulations were performed using 10 trials of matched trial designs with the Sim-NEUrCaucasian population in Simcyp V17. The ratios of mean AUC and clearance (CL) in cancer patients compared to healthy volunteers were calculated from the reported clinical studies and the simulated studies. In addition, the range of AUC and CL ratios were calculated using the maximum and minimum values from the reported studies in cancer patients and healthy volunteers.

Results

26 PK studies were collated for 8 Simcyp compounds in cancer patients, including probes substrates for CYP1A2, 2C8, 2C9, 2D6, 3A4 and Pgp. Figures 1 and 2 show the mean (± SD) observed and predicted AUC or CL in cancer patients for each substrate.

Conclusions

• The Sim-Cancer population for Simcyp V17 reasonably predicts the exposure and CL of probe substrates for CYP1A2, 2C8, 2C9, 2D6, 3A4 and Pgp in cancer patients (generally within 50% of observed values).
• The ratios of AUC and CL in cancer patients compared to healthy volunteers was generally predicted well (within 50% of observed values) when taking into account the different trial designs used for the studies in each population (e.g. ages).
• Based on these data CYP abundance appears to be similar in cancer patients to healthy volunteers and difference in PK are likely due to differences in the age of the trial subjects.
• High variability in the observed PK data has a large impact on the prediction accuracy of the difference in AUC and CL between cancer patients and healthy volunteers.

References


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