Background and Importance

Tyrosine kinase inhibitors (TKIs), like erlotinib and gefitinib, are widely used in anticancer therapy. However, after long term administration, resistance is observed in the majority of patients. Thus, it is necessary to be able to define individualized dosage regimens for TKIs in cancer patients. Nowadays, modeling and simulation approaches represent the most powerful tool in the hands of clinical pharmacists towards precision medicine.

Aim and Objectives

Population pharmacokinetic (PK) – pharmacodynamic (PD) modeling was utilized to simulate erlotinib and gefitinib dosage regimens for non-small cell lung cancer, as well as the corresponding efficacy. In silico clinical trials with virtual patients, of several resistance levels, were simulated in order to optimize pharmacotherapy and get better therapeutic outcomes.

Materials and Methods

The utilized PKPD model was obtained from the literature (1). This model was fully validated using statistical criteria and goodness of fit plots. The PK model for both erlotinib and gefitinib refers to a one-compartment model with first order absorption and elimination. This PK model was coupled with an additional PD model, which can capture the two types of tumor resistance:

a) Primary resistance referring to patients who do not respond to the TKI treatment and

b) Acquired resistance due to the progression of cancer, after an initial period of clinical benefit, while the patient is still under TKI treatment

A schematic representation of the entire PKPD model is depicted in Figure 1.

Results

Concentration vs. time and effect vs. time plots for the virtual patients were simulated for a variety of conditions and tumor resistance levels. In the following figures, the PD endpoint (i.e. tumor volume) is expressed in mm³, while the “time” scale refers to hours. Initially, the impact of multiple TKI administration on the plasma levels and efficacy was simulated (Figure 2).

Multiple dosing results in TKI accumulation in plasma, reaching steady state after 5-6 administrations and concomitantly tumor volume decreases.

The impact of altered clearance from the body is depicted in Figure 3:

Concentration vs. time and effect vs. time plots for the virtual patients were simulated for a variety of conditions and tumor resistance levels. In the following figures, the PD endpoint (i.e. tumor volume) is expressed in mm³, while the “time” scale refers to hours. Initially, the impact of multiple TKI administration on the plasma levels and efficacy was simulated (Figure 2).

Figure 2. Plasma profiles and tumor volume vs. time for three scenarios: A) Single administration, B) Four administrations ending at 96 h, C) Multiple dosing for one week (168 h) where inter-individual variability 20% was included in all PK & PD parameters.

Decrease of body clearance (Fig.3A) leads to higher plasma concentrations, as well as more intense effect (i.e. tumor volume shrinkage). Increased clearance (Fig.3B) results in rapid elimination and thus, the antitumor effect declines (tumor volume increases). The situation of treatment “failures” was also simulated. Figure 4A shows the case of a TKI treatment, once every two days, leading to tumor volume increases. In Fig.4B, both the resistant and the sensitive cancer cells were simulated to be more aggressive, resulting in larger tumors.

Figure 3. Plasma profiles and tumor volume vs. time for A) Low TKI clearance and B) High TKI clearance from the body. In all cases, inter-individual variability of 20% was set to all PK & PD parameters.

Conclusion and Relevance

In this study, the use of modeling techniques led to the simulation of many patients’ conditions and dosage regimens. Wider application of in silico methods using virtual patients will allow the design of the most appropriate individualized dosage schemes tailored to patients’ requirements.

References