A Physiologically-based Pharmacokinetic (PBPK) Approach to Evaluate Differences in Pharmacokinetics Between Healthy Subjects and Cancer Patients

Nageshwar R. Budha, Srawanti Cheeti, Sharmila Rajan, Mark J. Dresser, Amita Joshi, and Jin Y. Jin
Department of Clinical Pharmacology, Genentech, 1 DNA Way, South San Francisco, CA 94080

Background

- It is well-recognized that cancer patients are different from healthy volunteers (HV) with regards to age, plasma protein levels, concomitant medications etc. [1-3].
- Various population characteristics of the patient population such as age, height, weight, protein and hematocrit levels can affect ADME and PK of drugs.
- Therefore, accurate representation of the distribution of these population characteristics and the correlation among them in the target patient population is critical to predict the effect of intrinsic and extrinsic factors on the PK of drugs using the PBPK approach.
- Simcyp® is one of the software platforms available for mechanistic modeling and simulation of the absorption, distribution, metabolism, and excretion (ADME) of drugs in virtual patient population.

Objectives

- To characterize the population characteristics and their relationships in cancer patients
- To establish a custom population profile for Simcyp that can better predict PK and the effect of intrinsic and extrinsic factors on drug exposure in oncology

Methods

Establishment of Custom Population Profile for Cancer Patients

Data collection:
An oncology population database was established based on demographic (gender, age, height, and body weight) and lab (albumin, AAG, and hematocrit) data from 21 historical Genentech clinical trials in 2597 cancer patients.

Correlation of Population Characteristics:
- Mathematical models describing the distribution and relationship among population characteristics were obtained from the Simcyp healthy volunteer (HV) population profile (Simcyp® version 10.0, Simcyp, Sheffield, UK) and fitted to the observed data in the oncology population database.
- SigmaPlot (version 10.0, Systat Software, Inc.) was used for model fitting using nonlinear regression and to generate graphs.

Prediction of Population Characteristics:
- Simulations were conducted using 50 trials with 10 subjects per trial (total n=500) for the Simcyp HV and the oncology population profiles.
- The distribution of demographic and lab variables from the simulated trials were compared with observed data.
- All predictions and simulations were performed using Simcyp® version 10.0.

Prediction of PK
- PK of 7.5 mg midazolam and 1200 mg saquinavir in HV and cancer patients were predicted using the two population profiles.
- Simulations were conducted for 50 trials with 10 subjects per trial (total n=500).
- The plasma PK parameters (Cmax, AUC) of midazolam and saquinavir from PBPK simulations were compared in the two populations.

Results

Establishment of Custom Population Profile for Cancer Patients

Data collection:
An oncology population database was established based on demographic (gender, age, height, and body weight) and lab (albumin, AAG, and hematocrit) data from 21 historical Genentech clinical trials in 2597 cancer patients.

Correlation of Population Characteristics:
- Summary of parameters used in the custom oncology population profile are shown in Table 2 and correlations of population characteristics in the patient population are shown in Figure 1.

Table 1: Summary of Clinical Data in the Oncology Population Database

<table>
<thead>
<tr>
<th>Variable Type</th>
<th>Variable</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic</td>
<td>Gender</td>
<td>Proportion of Female 0.51 Observed</td>
</tr>
<tr>
<td>Lab</td>
<td>Age</td>
<td>Male: 1279, Female: 1318</td>
</tr>
<tr>
<td></td>
<td>Height</td>
<td>Male: 1279, Female: 1318</td>
</tr>
<tr>
<td></td>
<td>Body Weight</td>
<td>Male: 1279, Female: 1318</td>
</tr>
<tr>
<td>Disease Type</td>
<td>Phase I</td>
<td>Male: 224, Female: 549</td>
</tr>
<tr>
<td></td>
<td>Phase II</td>
<td>Male: 667, Female: 410</td>
</tr>
</tbody>
</table>

Table 2: Custom Oncology Population Profile

<table>
<thead>
<tr>
<th>Variable Type</th>
<th>Variable</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic</td>
<td>Age</td>
<td>Male: 1279, Female: 1318</td>
</tr>
<tr>
<td></td>
<td>Height</td>
<td>Male: 1279, Female: 1318</td>
</tr>
<tr>
<td></td>
<td>Body Weight</td>
<td>Male: 1279, Female: 1318</td>
</tr>
</tbody>
</table>

Table 3: PK Parameters of Midazolam (7.5 mg)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax</td>
<td>0.72 (0.619 - 0.804)</td>
<td>Observed</td>
</tr>
<tr>
<td>AUC</td>
<td>7.29 (5.759 - 8.849)</td>
<td>Observed</td>
</tr>
<tr>
<td>Cmax</td>
<td>0.72 (0.619 - 0.804)</td>
<td>Simcyp</td>
</tr>
<tr>
<td>AUC</td>
<td>7.29 (5.759 - 8.849)</td>
<td>Simcyp</td>
</tr>
</tbody>
</table>

Prediction of Midazolam PK:
- The PBPK simulations suggested that PK of midazolam (which is extensively metabolized by CYP3A4) are different in cancer patients compared to healthy subjects, consistent with the literature (Table 3).
- It has been shown in the literature that CYP3A activity did not change with age, sex, and body size measurements in 134 patients with advanced cancer [6], which supports the lack of difference in midazolam PK between the two populations.

Prediction of Saquinavir PK:
- The oncology population profile predicted higher plasma exposure for saquinavir compared to the HV population profile (Figure 3).
- The predicted mean Cmax (95% CI) in HV and cancer patients were 0.537 (0.492 - 0.582) mg/L and 0.674 (0.619 – 0.73) mg/L, respectively, following a 1200 mg single oral dose of saquinavir.
- Similarly, the predicted mean AUC (95% CI) in the two populations were 3.72 (3.35 – 4.11) mg·h/L and 5.09 (4.56 – 5.61) mg·h/L, respectively.

Possible reasons for higher exposure of saquinavir in patients compared to HV:
- MPGL (microsomal protein per gram of liver) gradually decrease with age resulting in reduced clearance (CL) of drugs that are eliminated via hepatic metabolism [13].
- Differences in plasma protein levels between the two populations:
  - Plasma levels of AAG are higher in cancer patients. Saquinavir PK could have been affected due free fraction.

Conclusions

- In summary, this work demonstrates the importance of a population profile specific for oncology due to various pathological differences in cancer patients compared to healthy subjects.
- The custom oncology population profile is a valuable addition to the scientific toolbox given its ability to accurately generate virtual oncology population to better predict PK using Simcyp.

References