Population Pharmacokinetics of Lapatinib in Cancer Patients

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Background

Lapatinib (Tykerb™) is a potent and selective inhibitor of the EGFR and HER2 tyrosine kinases. It is approved for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2.

Objectives

The aim of this study was to characterize the pharmacokinetics (PK) of lapatinib using sparse sampling in Phase II studies of patients with cancer and to identify patient characteristics that influence lapatinib pharmacokinetics.

Methods

Patients: A total of 290 cancer patients from the following 4 Phase I/II studies contributed 2025 plasma lapatinib concentrations.

1. Phase I single dose study in patients with solid tumors. A total of 27 male and female patients were dosed at 1500 mg under fasted conditions. Serial PK samples were taken for up to 48 hrs post dose.
2. Phase II study in patients with advanced or metastatic breast cancer. Patients received 1500 mg lapatinib once daily (QD) until disease progression, consent withdrawal or unacceptable toxicity. A total of 80 female patients provided sparse PK samples on both Day 1 and Day 28.
3. Phase II study in patients with advanced or metastatic breast cancer. Patients received 1500 mg lapatinib once daily (QD) or 500 mg lapatinib twice daily (BID) for 12 weeks. A total of 134 female patients provided sparse PK samples on both Day 1 and Day 28.
4. Phase II study in patients with advanced or metastatic non-small cell lung cancer. Patients received 1500 mg lapatinib once daily (QD) or 500 mg lapatinib twice daily (BID) for 12 weeks. A total of 49 male and female patients provided sparse PK samples on both Day 1 and Day 28.

Model development: Population pharmacokinetic analysis was conducted using a nonlinear mixed-effects modelling approach with NONMEM VI software. Patient demographics, liver function, concomitant medications, and diarrhea scores were evaluated for their influence on lapatinib PK. For continuous covariates, a power function was utilized ($TVP_i = \theta_1 \times (COV_i / COV_{Ref})^{\theta 2}$). For categorical covariates, the fractional change of the typical parameter value was estimated ($TVP_i = \theta_1 \times \theta_2^{COVi}$). The full covariate model was subject to backward elimination of insignificant or poorly estimated covariates. Visual predictive check (VPC) was performed for final model evaluation, in which two hundred simulations were run from the original dataset with the final model parameter estimates and the median and 95% prediction intervals were compared with the observed data.

Figure 1. Schematics of the Lapatinib PK Structural Model

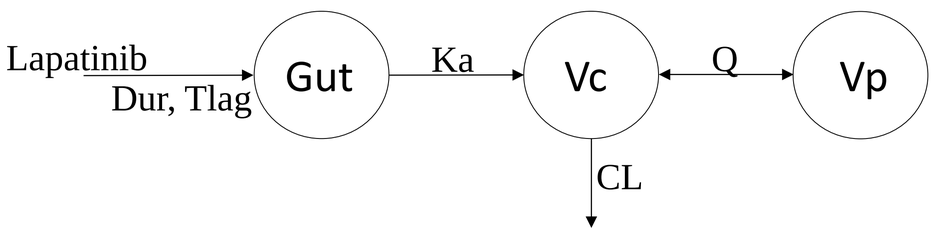


Table 1. Parameter Estimates of the Final PopPK Model

Model Parameters	Estimate	%RSE	CV%
KA (1/hr)	0.068	3.37	
CL/F (L/hr)	39	4.92	
VC/F (L)	46.5	13.7	
Q/F (L/hr)	11.3	11.1	
VQ/F (L)	338	7.51	
TLAG (hr)	0.206	22.6	
DUR (hr)	1.58	7.66	
Effect of Age (ref=50 yrs) on KA	-0.266	40.2	
Effect of Study1 on CL/F	2.66	21.5	
Effect of BID Dosing on CL/F	0.544	8.57	
Effect Hispanic Ethnicity on VC/F	1.6	17.1	
Effect Asian Race on F	1.24	7.6	
IIV(KA)	0.0503	23.1	22.4
IIV(CL/F)	0.198	17.7	44.5
IIV(VC/F)	0.817	13.3	90.4
IIV(TLAG)	1.03	28.3	101.5
IIV(DUR)	0.122	53.2	34.9
IOV(CL/F)	0.286	10.4	53.5
Proportional Residual Variability	0.0413	8.21	20.3
Additive Residual Variability	114	41.9	
Residual Scaling for Sparse PK	1.52	4.53	

Results

- Lapatinib PK were best described by a model with two distribution compartments, linear elimination from the central compartment, and a delayed zero-order input in sequence with a first-order absorption process (Figure 1).
- Lapatinib PK were influenced by race, age, and dosing frequency (Figure 2).
  - Oral bioavailability (F) was 28% higher in Asians than other races.
  - CL/F was 42% lower with BID dosing than QD dosing.
  - VC/F was 61% higher in Hispanics than other racial/ethnic groups.
  - KA decreased with age.
- Moderate to high inter-individual and inter-occasion (between Day 1 and Day 28) variability in CL/F and VC/F was observed (Table 1)
- Drug induced diarrhea was not found to influence lapatinib PK (Figure 3).

Figure 2. Influence of Covariates on Lapatinib PK (Top: Base model; Bottom: Final model)

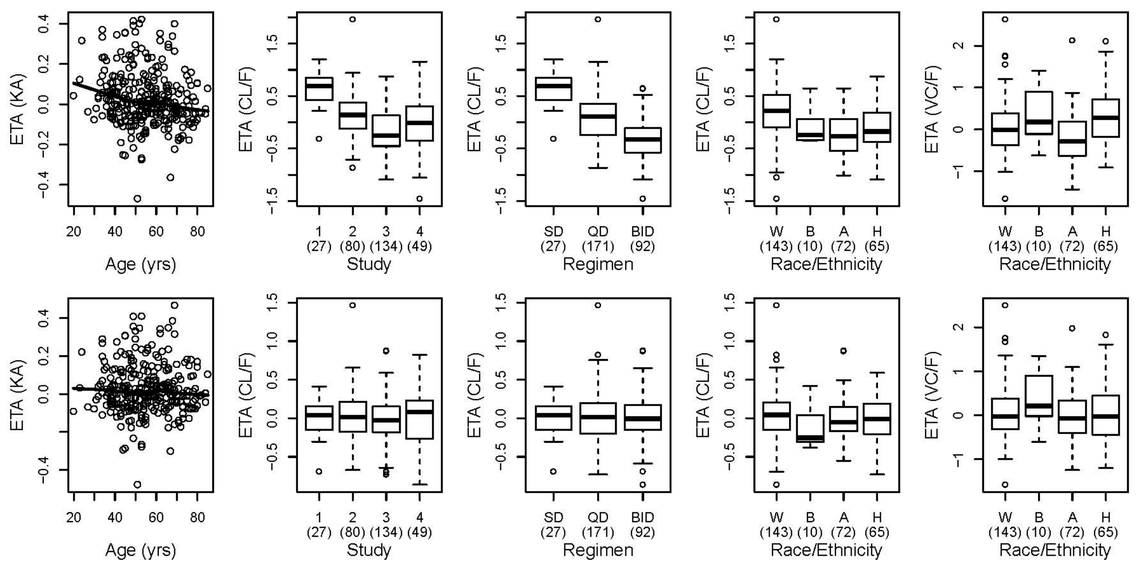


Figure 3. Impact of Diarrhea on Lapatinib PK

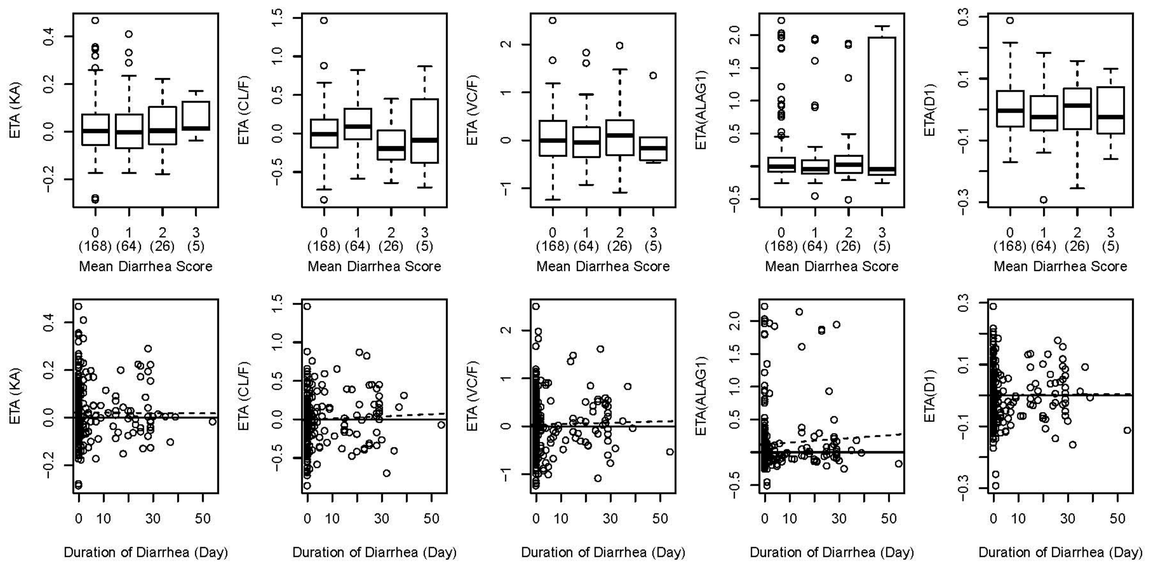


Figure 4. Diagnostic Plots of the Final PopPK Model

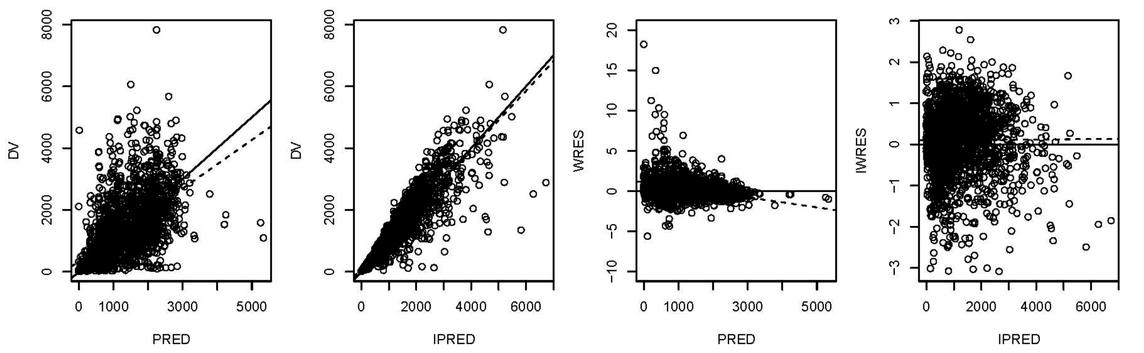
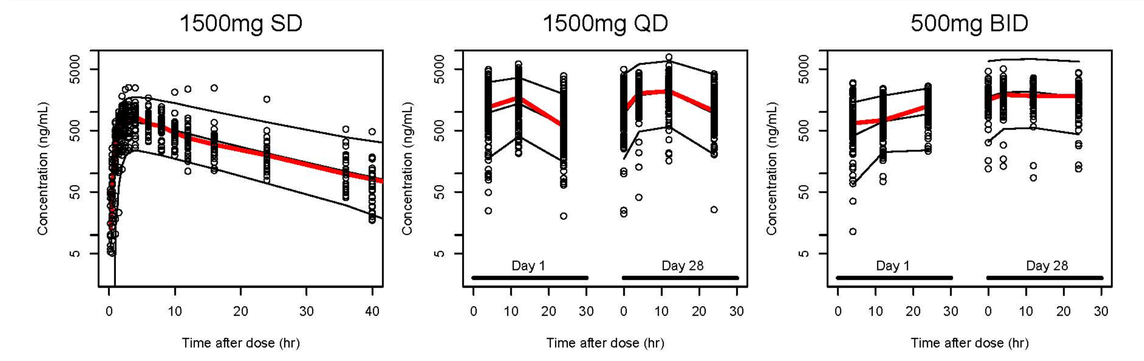


Figure 5. Visual Predictive Check



Conclusions

The population PK model developed in this analysis adequately characterized the pharmacokinetics of lapatinib which enabled identification and quantification of patient characteristics that influence lapatinib exposure. The model will allow further analysis of the relationship between lapatinib exposure and tumor response in patients with breast cancer.