Population Pharmacokinetics of Cetuximab in Patients With Squamous Cell Carcinoma of the Head and Neck

Nathanael L. Dirks, PharmD, Arno Nolting, PhD, Andreas Kovar, PhD, FCP, and Bernd Meibohm, PhD, FCP

Cetuximab is a monoclonal antibody directed against the epidermal growth factor receptor and is indicated in the treatment of squamous cell carcinoma of the head and neck. The population pharmacokinetics of cetuximab were characterized by nonlinear mixed effects modeling (NONMEM V) using a total of 912 concentrations from 143 patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck enrolled in 2 phase I/II studies. Cetuximab pharmacokinetics were best described by a 2-compartment model with Michaelis-Menten-type saturable elimination. Population estimates (between-subject variability, percent coefficient of variation) of the pharmacokinetic parameters were $V_{\text{max}}$ 4.38 mg/h (15.4%), $K_m$ 74 μg/mL, central compartment volume $V_1$ 2.83 L (18.6%), peripheral compartment volume 2.43 L (56.4%), and intercompartmental clearance 0.103 L/h (97.2%). Ideal body weight and white blood cell count were identified as predictors of $V_{\text{max}}$ and total body weight as a predictor of $V_1$. Clinical dose adjustments beyond the approved body surface area–based dosing of cetuximab may be warranted in patients with extreme deviations of their actual body weight from ideal body weight. Agreement between simulated and measured concentrations monitored for up to 43 weeks of therapy indicates that cetuximab pharmacokinetic parameters remained constant during prolonged therapy.

Keywords: Cetuximab; population pharmacokinetics; cancer; squamous cell carcinoma; monoclonal antibody; biologic; protein therapeutic

Journal of Clinical Pharmacology, 2008;48:267-278
© 2008 the American College of Clinical Pharmacology

Cetuximab is a recombinant, human/mouse chimeric IgG1 monoclonal antibody that binds specifically to the extracellular domain of the human epidermal growth factor receptor (EGFR; also known as ErbB-1/HER1). By binding to EGFR, cetuximab prevents the binding of endogenous ligands such as epidermal growth factor (EGF) and transforming growth factor-α. This blockade prevents EGFR signaling, which is intricately involved in multiple processes involved in tumor growth and metastasis, such as cell proliferation, cell differentiation, cell survival, cell migration, tumor angiogenesis, and DNA repair. Cetuximab can also induce internalization and subsequent degradation of EGFR, leading to downregulation of cell surface EGFR and a reduction in EGFR signaling. Cetuximab is currently indicated in squamous cell carcinoma of the head and neck (SCCHN) and EGFR-expressing metastatic colorectal cancer. It is approved as a single agent in both cancers, as well as in combination therapy with radiation therapy for SCCHN and with irinotecan for colorectal cancer.

In early phase I studies, attempts to characterize the pharmacokinetics of cetuximab indicated that it exhibits nonlinear or Michaelis-Menten-type...
elimination.\textsuperscript{8,9} This nonlinearity was attributed to saturation of the EGFR-mediated endocytosis of cetuximab, a clearance pathway that entails internalization and degradation of the EGFR/cetuximab complex.\textsuperscript{10} While this nonlinear elimination pathway seems to be largely saturated at therapeutic concentrations, a second, nonspecific elimination pathway that is not saturable at therapeutic concentrations seems to be the major determinant for cetuximab elimination during therapy with approved cetuximab doses.\textsuperscript{11} The resulting elimination half-life estimates at therapeutic concentrations range between 66 and 97 hours at the approved dosing regimen of a 400-mg/m\textsuperscript{2} initial dose, followed by weekly doses of 250 mg/m\textsuperscript{2}, but increase from 33.3 to 119.4 hours after single cetuximab doses of 20 to 500 mg/m\textsuperscript{2}.\textsuperscript{11}

Although cetuximab concentrations have been correlated with antitumor activity,\textsuperscript{12} most reports on cetuximab pharmacokinetics have been limited to noncompartmental analyses, and the population pharmacokinetics of cetuximab have not been published in the literature except in abstract format for an analysis conducted for regulatory purposes.\textsuperscript{7,11}

Thus, this article describes a population pharmacokinetic analysis based on data from 2 clinical trials in patients with SCCHN. The objectives of this analysis were (1) to determine the typical population pharmacokinetic parameters for cetuximab and their between-subject variability and (2) to identify covariates that are significant predictors for cetuximab systemic exposure and to assess their potential implications for clinical dosing.

**METHODS**

**Study Design and Patient Population**

Cetuximab serum concentration-time data were obtained from 2 studies, EMR 62202-008 (study A) and EMR 62202-016 (study B), that are described elsewhere in detail.\textsuperscript{13,14} Both studies were conducted in compliance with the Declaration of Helsinki and the Guidelines for Good Clinical Practice. Written informed consent was obtained from all subjects.

Study A was a randomized, multicenter phase I/II study (n = 53) to evaluate the safety and tolerability of cetuximab (Erbitux) in combination with platinum and 5-fluorouracil (5-FU) as first-line treatment in patients with recurrent and/or metastatic SCCHN, as well as to evaluate the pharmacokinetics of cetuximab under coadministration with platinum.\textsuperscript{13} Main inclusion criteria were stage III/IV recurrent or metastatic disease not suitable for local therapy, Karnofsky performance status $\geq 70$, and adequate hematologic, liver, and renal function. Cetuximab was administered as an initial dose of 400 mg/m\textsuperscript{2} infused over 2 hours, followed by weekly doses of 250 mg/m\textsuperscript{2} given over 1 hour. Patients were randomized to receive either cisplatin 100 mg/m\textsuperscript{2} on day 2 of the chemotherapy cycle or carboplatin AUC 5 (target area under the curve of 5 mg/mL-min) on day 1 of the cycle. 5-FU was administered as a continuous infusion on day 1 for the duration of 120 hours at the assigned dose levels of 600, 800, and 1000 mg/m\textsuperscript{2}/day. Chemotherapy (5-FU and platinum) cycles were repeated every 3 weeks. The primary treatment phase duration was 6 weeks (2 cycles), but patients were allowed to continue with treatment if they benefited from the initial treatment phase. Of the 53 patients enrolled into the study, 38 completed the primary treatment phase. Peak and trough cetuximab concentrations were obtained at weeks 2 to 4 of therapy. In addition to the peak and trough obtained on week 4, a full concentration-time profile was obtained with sampling at 3, 6, 10, 24, 48, 72, 96, and 168 hours after the start of cetuximab administration.

Study B was a multicenter phase II study (n = 103) to evaluate the efficacy and toxicity of cetuximab (Erbitux) monotherapy in patients with platinum-refractory recurrent and/or metastatic SCCHN, as well as to investigate the pharmacokinetics of cetuximab.\textsuperscript{14} Main inclusion criteria were stage III/IV recurrent or metastatic disease, a Karnofsky performance status $\geq 70$, and adequate hematologic, liver, and renal function. Patients were to receive cetuximab as an initial infusion of 400 mg/m\textsuperscript{2} followed by weekly infusions of 250 mg/m\textsuperscript{2} for at least 6 weeks, if possible. If they responded to treatment or had stable disease, treatment was continued until disease progression, clinical deterioration, or unacceptable side effects were observed. On occurrence of disease progression or clinical deterioration, salvage treatment was offered with cetuximab (250 mg/m\textsuperscript{2} weekly) plus the same platinum regimen the patient was on prior to receiving cetuximab monotherapy. Of the 103 patients treated with cetuximab monotherapy, 53 subsequently received combination therapy. Cetuximab peaks and troughs were obtained at weeks 1, 4, and 6 during monotherapy. If the patient entered the combination therapy phase, cetuximab peaks and troughs were obtained again at weeks 1, 4, and 6 after switching to combination therapy. A sample
was also taken at the end-of-study visit, which was up to 6 weeks after the last dose of cetuximab was administered. The total study period ranged from 0.1 to 56 weeks with a median of 14 weeks.

Assay Methodology

Cetuximab serum concentrations were determined using a validated sandwich enzyme-linked immunosorbent assay (ELISA). In brief, serum samples were diluted by a factor of 500 and added to microtiter plates coated with the extracellular domain of EGFR, which served as the capture antigen. After incubation, plates were washed with buffer and further incubated with rabbit antihuman IgG conjugated with horseradish peroxidase, which binds to the cetuximab immobilized in the microtiter plates. Unbound conjugate was removed, and tetramethylbenzidine, a substrate for horseradish peroxidase, was added. Tetramethylbenzidine was oxidized to a colored product, the absorbance of which was measured by a plate reader at 450 nm. This absorbance was directly related to the cetuximab concentration in the serum sample. The lower and upper limits of quantification were 0.5 ng/mL and 15 ng/mL for the diluted cetuximab samples, corresponding to 0.25 and 7.5 μg/mL for undiluted samples. Serum samples with higher concentrations of cetuximab were further diluted to fit into the linear calibration range. Accuracy of the assay was between 98.5% and 104%, and the precision ranged from 2.2% to 6.3%.

Population Pharmacokinetic Analysis

The population pharmacokinetic analysis was performed by nonlinear mixed effects modeling using a NMQual (Metrum Institute, Augusta, Maine) installation of NONMEM (Version V, level 1.1; Icon Development Solutions, Ellicott City, Maryland) under Compaq Visual Fortran (Version 6.5; Compaq Corporation, Houston, Texas). Xpose, Census, and S-Plus (Version 7.0; Insightful Corporation, Seattle, Washington) were used for data management and visualization. The first-order conditional estimation method (FOCE) within NONMEM was used throughout the model-building process. Across the 2 studies, most of the concentration measurements were within the first 8 weeks of cetuximab therapy. Therefore, the database was split with concentration data obtained during the first 8 weeks used for model building (model-building data set) and the remaining data for model qualification (model evaluation data set). Sampling times in the model evaluation data set ranged from weeks 10 to 43. The structural model was evaluated using only the densely sampled data from study A. The covariate model was subsequently built using data from both studies. All concentration data were log transformed prior to the analysis, and the residual variance model was modified accordingly (transform-both-sides approach). Log transformation of the data stabilized the convergence of the structural models and resulted in shorter run times.

Six structural models, including 1- or 2-compartment models with linear, nonlinear, or parallel linear and nonlinear elimination pathways, were evaluated based on minimization of the Akaike information criterion (AIC) value, precision and plausibility of parameter estimates, and a number of goodness-of-fit plots. The AIC was defined in terms of the objective function value (OFV) and number of parameters (p) in the model: AIC = OFV + 2p. Prior information about the pharmacokinetics of cetuximab from phase I and phase II trials, such as the presence of nonlinear elimination, was also taken into account while building the structural model.

Between-subject variability in cetuximab pharmacokinetic parameters was assumed to follow a lognormal distribution and was modeled according to an exponential error model. During the model-building procedure, between-subject variability for parameters was assumed to be uncorrelated, and only the diagonal elements of the variance-covariance matrix were estimated. Once the final model was determined, the addition of covariance terms was evaluated. Due to the unbalanced sampling design of the 2 studies and their performance in different clinical settings, separate residual error models were used per study. Residual variability was modeled using a log-transformed exponential error model.

Twenty-one potential covariates were evaluated. The covariates were composed of (1) demographic and anthropometric measurements (gender, age, ethnicity, total body weight [WGT], ideal body weight [IBW], body surface area [BSA], and clinical study), (2) blood chemistry and hematology measurements (blood urea nitrogen, serum creatinine, creatinine clearance, total bilirubin, albumin, aspartate and alanine aminotransferases, and white blood cell [WBC] count), and (3) concomitant therapy and disease-related factors (EGFR expression, presence of human antichimeric antibodies, concomitant platinum and/or 5-FU therapy, Karnofsky function score, and duration of cetuximab therapy). Covariates were updated over time in the observation records for each patient when the respective data were available.
Before building the covariate model, all potential covariates were plotted against each other to identify any high intercorrelation, as to avoid simultaneous inclusion of correlated predictors. Inclusion of a covariate-parameter relationship was based on the likelihood ratio test. The criterion for including a covariate in the model during the forward addition steps was a decrease in the objective function value of 3.84 (\(P < .05\)). During the backward deletion steps, an objective function change of 10.83 (\(P < .001\)) was required for a covariate to remain in the model. A more stringent criterion was used during the backward deletion steps because of the multiple comparisons made during the forward portion of stepwise covariate modeling. Covariate modeling was also guided by goodness-of-fit plots and changes in between-subject variability.

A stratified approach to the univariate analysis was taken during the forward addition step of the covariate modeling, in that size covariates (IBW, WGT, BSA) were first evaluated and included in the model. Once the effect of size on cetuximab pharmacokinetics had been accounted for, the remaining covariates were evaluated in the model. The stratified approach was taken as correlation often exists between size covariates and nonsize covariates (eg, gender and weight). Such correlations can mask covariate relationships and lead to difficulties interpreting the effects of 2 correlated covariates. Stepwise backward deletion was conducted once the full model was established.

Relationships between continuous covariates and pharmacokinetic parameters were modeled using linear proportional (equation (1)) and power (nonlinear) models (equation (2)) with the covariate (COV) normalized to the population median for the data set. Categorical covariates were modeled as shown in equation (3):

\[
P = \theta_1 \times (1 + \theta_2 \times (COV - \text{Median})),
\]

where the \(\theta\)s are the parameters to be estimated, and \(\theta_1\) represents the typical value of a pharmacokinetic parameter (P) in an individual with the median value for the covariate.

Model Qualification

The ability of the final population pharmacokinetic model to adequately describe the observed data in the model-building data set was evaluated using a predictive check. Cetuximab peak and trough concentrations at week 4 of therapy served as the metrics of interest. The final population pharmacokinetic model and parameter point estimates were used to perform Monte Carlo (parametric) simulations of the metrics of interest. The model evaluation data set with concentration data beyond week 8 was used to evaluate the ability of the final population pharmacokinetic model to predict cetuximab concentrations in an independent data set. Nonparametric bootstrap analysis was used to evaluate the precision and stability of the final model parameter estimates. Patients were randomly sampled with replacement from the model-building data set used for building the population pharmacokinetic model to create bootstrap data sets with the same sample size as the original. A stratified sampling approach was used in that the ratio of patients from the 2 studies was kept constant.

RESULTS

Data

A total of 143 patients provided evaluable pharmacokinetic data for the population analysis: 47 from study A and 96 from study B. Table I summarizes the demographics for these patients. The majority of patients (138/143) had EGFR-expressing tumors determined by immunohistochemical evaluation. The presence of human antichimeric antibodies was not detected in any of the patients participating in the 2 studies.

The initial cetuximab data set consisted of 1142 concentration measurements. There were 86 baseline observations prior to the first cetuximab administration, which were defined as 0 and removed from the data set before log transformation. After splitting the database into model-building and model evaluation data sets, 912 concentrations remained for building the population pharmacokinetic model: 530 from study A and 382 from study B. Due to the unbalanced sampling schedule between the 2 studies, study A patients contributed a median of 13 data points per individual, whereas study B patients contributed a median of 4 data points per individual.

Structural Model

Cetuximab serum concentrations were best described by a 2-compartment model with nonlinear elimination,
based on AIC values and goodness-of-fit plots. Compared with a 1- or 2-compartment model with linear elimination, the corresponding model with nonlinear elimination resulted in further reduction of the AIC value. The goodness-of-fit plots indicated that the nonlinear model provided a better fit to lower concentrations (<75 μg/mL) than the linear model. In addition, the results from prior pharmacokinetic studies supported the use of a nonlinear elimination model.8-10 Addition of a second, linear elimination pathway to the nonlinear model resulted in no change in the objective function value. The goodness-of-fit plots between the nonlinear model and parallel elimination model were very similar. This lack of improvement in fit to the data with the parallel elimination model led to selection of the more parsimonious nonlinear model as the structural base model. Regardless of the elimination pathways, a 2-compartment model always provided a better fit to the data than a 1-compartment model based on AIC values and goodness-of-fit plots.

The 2-compartment, nonlinear elimination model was parameterized in terms of $V_{\text{max}}$ (maximum elimination rate), $K_m$ (cetuximab concentration at which the elimination is at half maximum), $V_1$ (volume of central compartment), $V_2$ (volume of peripheral compartment), and $Q$ (intercompartmental clearance).

The initial structural model was unable to account for between-subject variability in both $V_{\text{max}}$ and $K_m$, even after addition of a covariance term for both parameters. Based on the hypothesis that physiologically, there should be more variability among individuals with regard to $V_{\text{max}}$ than $K_m$, the $K_m$ parameter was treated as a fixed value across all subjects, which resulted in an objective function increase of only 0.3 points and improvement of the precision for the estimate of between-subject variability in $V_{\text{max}}$.

Once the base model was determined, data from study A and B were pooled together for the covariate modeling. Separate residual error models were used for each study, which added stability to the minimization procedure and resulted in a change in objective function value ($\Delta$OFV) of –32.8, as well as a decrease in between-subject variability estimates for all parameters.

### Covariate Model

The effect of covariates on cetuximab pharmacokinetics was first investigated for size measures with the purpose of identifying which, if any, are the most influential. The $\Delta$OFV indicated that linearly related IBW ($\Delta$OFV –29) was the most important size covariate for $V_{\text{max}}$ versus BSA ($\Delta$OFV –14) and WGT ($\Delta$OFV –9). Inclusion of IBW reduced the between-subject variability in $V_{\text{max}}$ from 23.6% to 17.9% (percent coefficient of variation [%CV]). Based on $\Delta$OFV, linearly related WGT was found to be the most important size covariate on both $V_1$ and $V_2$. Inclusion of WGT on $V_1$ resulted in an $\Delta$OFV of –22.7 and a decrease in

### Table I  Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, male/female</td>
<td>120/23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnicity, Caucasian/unknown</td>
<td>131/12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study, A/B</td>
<td>47/96</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant 5-FU,a yes/no</td>
<td>47/96</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant platinum,a yes/no</td>
<td>89/54</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>56</td>
<td>23-77</td>
<td></td>
</tr>
<tr>
<td>Duration of cetuximab therapy, wk</td>
<td>6</td>
<td>1-54</td>
<td></td>
</tr>
<tr>
<td>Weight, kg</td>
<td>60</td>
<td>34-113</td>
<td></td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>1.7</td>
<td>1.2-2.2</td>
<td></td>
</tr>
<tr>
<td>Ideal body weight, kg</td>
<td>64.2</td>
<td>43.3-81.3</td>
<td></td>
</tr>
<tr>
<td>White blood cell count, 10⁹/L</td>
<td>6.8</td>
<td>1.7-41.8</td>
<td></td>
</tr>
<tr>
<td>Blood urea nitrogen, mg/dL</td>
<td>23</td>
<td>4-106</td>
<td></td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>0.9</td>
<td>0.4-1.9</td>
<td></td>
</tr>
<tr>
<td>Creatinine clearance, mL/min</td>
<td>74</td>
<td>22-167</td>
<td></td>
</tr>
<tr>
<td>Total bilirubin, mg/dL</td>
<td>0.5</td>
<td>0.2-1.4</td>
<td></td>
</tr>
<tr>
<td>Albumin, g/dL</td>
<td>3.9</td>
<td>1.3-4.8</td>
<td></td>
</tr>
<tr>
<td>Aspartate aminotransferase, U/L</td>
<td>18</td>
<td>5-150</td>
<td></td>
</tr>
<tr>
<td>Alanine aminotransferase, U/L</td>
<td>14</td>
<td>1-64</td>
<td></td>
</tr>
<tr>
<td>Karnofsky function score</td>
<td>80</td>
<td>60-100</td>
<td></td>
</tr>
</tbody>
</table>

a. Patient received concomitant 5-fluorouracil (5-FU) or platinum chemotherapy at some point during the trial.
between-subject variability for $V_1$ from 21% to 18.3%. Adding WGT as a covariate on $V_2$ resulted in an $ΔOFV$ of −9.7 and a decrease in between-subject variability for $V_2$ from 54.1% to 46.6%. No effect of size covariates was identified for $Q$ or $K_m$.

The remaining covariates were screened using general additive modeling and plots of individual empirical Bayes estimates of the parameters versus each of the covariates. The general additive modeling only identified WBC as a covariate on $V_{\text{max}}$, whereas graphical analysis identified the same relationship as well as a potential effect of gender on $V_{\text{max}}, V_1$, and $V_2$. Modeling $V_{\text{max}}$ as a linear function of WBC resulted in an $ΔOFV$ of −37.0 and decreased the between-subject variability for $V_{\text{max}}$ further to 15.3%. No effect of gender was identified for $V_{\text{max}}$ ($ΔOFV$ −0.3) or $V_2$ ($ΔOFV$ −2.4). Adding gender as a covariate for $V_1$ resulted in an $ΔOFV$ of −6.4 but reduced the between-subject variability only from 18.7% to 17.8%. The estimated difference in $V_1$ between men and women was small (13.5% smaller $V_1$ for women). Subsequently, the effect of gender on $V_1$ did not pass the criterion for backward deletion and was removed from the model. The effect of WGT on $V_2$ was also removed during the backward deletion step, but all other covariates were retained in the model. The addition of covariance terms between $V_{\text{max}}$ and the volume parameters was investigated with the final model but did not result in any improvement.

The final population pharmacokinetic model and parameter estimates are presented in Table II. Goodness-of-fit plots for the final model are shown in Figure 1, and model-predicted and measured cetuximab concentration-time profiles for representative patients are provided in Figure 2. The estimates for $V_{\text{max}}$ and $K_m$ for a typical patient with median covariate values, as defined in the model, were 4.38 mg/h and 74 μg/mL, respectively. Between-subject variability in the parameters was relatively small for $V_{\text{max}}$ (15.4%) and $V_1$ (18.6%) but was larger for $V_2$ (56.4%) and $Q$ (97.2%). Ideal body weight and WBC accounted for almost 35% of the total variability in $V_{\text{max}}$, and WGT accounted for approximately 10% of the variability in $V_1$. The estimate of the proportional residual variance for study A (14.6%) was less than that for study B (21.2%), which may be attributed to the highly unbalanced sampling designs of the 2 studies.

Model Qualification

The precision of model parameter estimates was assessed by 500 nonparametric bootstrap replicates. As shown in Table II, the 90% confidence intervals were relatively tight and indicated good precision of most parameter estimates. The median population estimates obtained from the nonparametric bootstrap were generally within 5% of the estimates from the final model (data not shown), indicating that the final population model was stable. Furthermore, the 95% confidence intervals for the covariate effects did not overlap with 0, indicating the statistical significance of the covariates included in the final model.

The model was further evaluated using a predictive check for the model-building data set and simulation.
of concentrations in the model evaluation data set. For both model qualification methods, 500 Monte Carlo simulated data sets were created and compared with the observed peak and trough concentrations at week 4 for the model-building data set (Figures 3-4) and beyond week 8 for the model evaluation data set (Figure 5), respectively. The model adequately described general tendencies of peak and trough concentrations and the between-subject variability of peaks at week 4 in the model-building data set (Figure 4) and beyond week 8 of therapy in the model evaluation data set (Figure 5). Figure 3, however, indicates that the model overpredicted the between-subject variability in trough concentrations at week 4 at the lower concentrations, suggesting that 1 or more of the variance components of the model were overestimated. This is reflected in Figures 4 and 5, in which less than 10% of the trough observations fell outside the simulated 90% prediction interval.

For the model evaluation data set, the median prediction error (MPE) and median absolute prediction error (MAPE) were calculated using the individually predicted and observed concentrations beyond week 8. The MPE was –0.1% and 0.3%, and the MAPE was 2.9% and 6.8% for peak and trough concentrations, respectively, indicating that the predictions were generally unbiased and relatively precise.

DISCUSSION

Monoclonal antibodies often exhibit nonlinear pharmacokinetics presumably attributable to target-mediated elimination pathways via interaction with
The binding of cetuximab to the membrane receptor EGFR presents a specific, saturable elimination mechanism by which the cetuximab/EGFR complex is internalized and either degraded or recycled with recurrence of the receptor at the cell surface. This receptor-mediated endocytosis likely contributes a significant portion to the total clearance of cetuximab, given that EGFR is widely expressed in a variety of tissues. Panitumumab, another monoclonal antibody targeted toward EGFR, also exhibits nonlinear pharmacokinetics attributed to saturation of EGFR-mediated clearance. The effect of target-mediated clearance on monoclonal antibodies has also been observed for other membrane targets.

The saturable, nonlinear pharmacokinetics of cetuximab have been well characterized in phase I studies where cetuximab clearance was shown to decrease with increasing doses in the range of 20 to 200 mg/m². Likewise, in the current population analysis, we found that a 2-compartment model with nonlinear elimination provided the best fit to the data. Phase I studies also showed that at doses of 200 mg/m² and greater (up to 500 mg/m²), the estimated clearance for cetuximab levels off. The biphasic nature of cetuximab clearance versus dose suggests the presence of a nonsaturable first-order process in parallel to the EGFR-mediated elimination described above. This nonspecific linear elimination process is common for all antibodies and is likely due to slow proteolytic degradation from interaction between the Fc region of the antibody and Fc-receptors on hepatic cells or cells of the reticuloendothelial system. An attempt was made to model this parallel elimination process by building a model with both linear and nonlinear elimination pathways as it has

![Cetuximab serum concentration-time profile in 6 representative patients](image-url)
previously been used in the pharmacokinetic analysis of other monoclonal antibodies, including sibrotuzumab and panitumumab.\textsuperscript{24,27} The parallel elimination model did not offer a significant improvement in describing the data over the simpler nonlinear model likely because the data did not support the more complex model. Certainly, a limitation to this analysis was that dose escalation data were not available as all patients included in the analysis were treated at the same clinically approved dose level. Such data might have supported the more complex parallel elimination model and even helped further define
the population estimates and between-subject variability for $V_{\text{max}}$ and $K_m$.

Based on the final population pharmacokinetic model, cetuximab distributes into a central compartment volume ($V_1$) of 2.83 L for a patient weighing 60 kg, which is approximately equal to the plasma volume. The volume of distribution at steady state ($V_1 + V_2$) of 5.26 L for a 60-kg patient suggests an apparently limited distribution outside the vascular space, which is in line with the results from cetuximab phase I studies and consistent with the behavior of endogenous IgG immunoglobulins and other therapeutic monoclonal antibodies. Nevertheless, cetuximab is able to distribute to its target as evidenced by immunohistochemistry studies and EGFR tyrosine kinase assays, which showed almost complete EGFR saturation in tumor tissue samples obtained from patients with SCCHN receiving the approved doses of cetuximab.

The results of the predictive check and simulations revealed that the population pharmacokinetic model adequately described the central tendencies of peak and trough concentrations at week 4 in the model-building data set and beyond week 8 in the model evaluation data set. The model was able to adequately account for the between-subject variability in peak concentrations, but the variability in trough concentrations was overpredicted toward lower concentrations, as indicated by the disparity between the 25th percentiles (Q1) for observed and simulated trough concentrations data in Figure 3. Given that $V_{\text{max}}$ significantly influences trough concentrations, overestimation of the between-subject variability in $V_{\text{max}}$ may be the cause for this deviation.

Binding of cetuximab to EGFR induces internalization of the receptor, which is believed to lead to EGFR downregulation. Given the role EGFR plays in the elimination of cetuximab, one might hypothesize that with downregulation of EGFR, there may also be a decrease in cetuximab clearance over time. Based on the Monte Carlo simulations for the model evaluation data set, however, the population pharmacokinetic model was able to adequately describe cetuximab peak and trough concentrations beyond 8 weeks of therapy. This finding suggests that the elimination pharmacokinetics of cetuximab remain relatively stable over time during prolonged therapy. It is further supported by findings from a phase I study, in which no statistically significant change in clearance values was found between the first and fourth weekly dose of cetuximab.

An interesting and unexpected covariate relationship identified in our analysis is the influence of WBC on $V_{\text{max}}$. There is evidence in the literature, however, that lymphocytes, monocytes, macrophages, and neutrophils do express EGFR. This suggests that these cells may be involved in the receptor-mediated clearance of cetuximab. The final population pharmacokinetic model predicted a 2.2% change in $V_{\text{max}}$ per unit (10^9/L) change in WBC from the median WBC (6.8 x 10^9/L). Over the normal range of WBC (~4-11 x 10^9/L), the typical value for $V_{\text{max}}$ would vary from 4.1 to 4.8 mg/h, representing a ~6.4% and +9.6% change from the population mean $V_{\text{max}}$, respectively. The modest change in $V_{\text{max}}$ over the range of normal WBC would not likely necessitate a change in dosing, even in patients who develop leukopenia due to concomitant chemotherapy.

Size covariates are probably the most frequently identified covariates in population pharmacokinetic analyses and are well established as predictors of systemic exposure for small-molecule drugs as well as therapeutic monoclonal antibodies. In this analysis, 3 different size covariates (IBW, WGT, and BSA) were evaluated. IBW was found to be a better predictor of $V_{\text{max}}$ than BSA and WGT. As interactions with EGFR as well as Fc-receptors resulting in receptor-mediated endocytosis are assumed to be the major elimination pathways of cetuximab, our results suggest that the number of these receptors in its distribution space is better reflected by IBW than any of the other body size measures. This observation is not unexpected as the elimination capacity of at least the liver and the reticuloendothelial system as major sites of Fc-receptor-mediated elimination of monoclonal antibodies is only marginally affected by deviations of weight from IBW. The final model predicted a 1.1% change in $V_{\text{max}}$ per kg IBW deviation from the median IBW of 64 kg. The estimated changes from the typical population $V_{\text{max}}$ (4.38 mg/h) for patients with IBW varying from the observed minimum (43.3 kg) to the maximum IBW (81.3 kg) were ~22.4% (3.4 mg/h) and +18.7% (5.2 mg/h), respectively.

Although $V_{\text{max}}$ as a direct determinant of cetuximab clearance is best predicted by IBW, clinical dosing of cetuximab is currently performed based on BSA following the traditional standard practice of dosing in oncology. To visualize the impact of dosing based on BSA rather than IBW, consider a 6-foot-tall male patient whose body weight is 77.6 kg, which is also his IBW. Based on BSA calculated according to DuBois and DuBois and BSA calculated for patients with normal B1W varying from the observed minimum (43.3 kg) to the maximum IBW (81.3 kg) were ~22.4% (3.4 mg/h) and +18.7% (5.2 mg/h), respectively.

Now suppose the above patient has lost 20% weight (62 kg body weight; 80% of IBW) or even 35% body weight (50.4 kg body weight; 65% of IBW). His BSA-based cetuximab maintenance dose would be 498 mg (250 mg/m²). However, the population estimates and between-subject variability for $V_{\text{max}}$ and $K_m$. This suggests that these cells may be involved in the receptor-mediated clearance of cetuximab. The final population pharmacokinetic model predicted a 2.2% change in $V_{\text{max}}$ per unit (10^9/L) change in WBC from the median WBC (6.8 x 10^9/L). Over the normal range of WBC (~4-11 x 10^9/L), the typical value for $V_{\text{max}}$ would vary from 4.1 to 4.8 mg/h, representing a ~6.4% and +9.6% change from the population mean $V_{\text{max}}$, respectively. The modest change in $V_{\text{max}}$ over the range of normal WBC would not likely necessitate a change in dosing, even in patients who develop leukopenia due to concomitant chemotherapy.
16.7% lower—but our population pharmacokinetic model would predict the same $V_{\text{max}}$ for both situations, leading to a reduced systemic exposure of cetuximab in the underweight patient. The modest impact of this effect, however, indicates that the approved BSA-based dosing regimen for cetuximab provides consistent systemic exposure in clinical use even in subjects with substantial deviation between their actual body weight and IBW. Only in very extreme cases of severe underweight might standard dosing need to be adjusted to avoid underdosing of the patient.

The potential clinical relevance of this finding is supported by the prominence of underweight in patients with advanced stages of solid tumors, including SCCHN. In fact, in the patient population used for this analysis, almost 25% of the patients weighed less than 80% of IBW. A comparison of the trough concentrations at 4 weeks and beyond in these patients with the troughs of the other patients in our analysis indicated that the troughs were indeed lower in the underweight group (median 48.2 vs 62.4 μg/mL, $P = .014$). This finding supports the selection of IBW as predictor for cetuximab elimination rather than BSA or WGT. Our results are furthermore in agreement with a previous report that suggests that dosing based on BSA may have limitations for some monoclonal antibodies.27

Fracasso et al16 recently reported a correlation between cetuximab trough levels and antitumor response on cetuximab monotherapy. Patients with partial response/stable disease tended to have higher average trough levels compared to those with progressive disease (mean 60.7 vs 33.2 μg/mL, $P = .002$). Although these study results were based on a small number of patients ($n = 33$) with different cancer types (predominantly colorectal, breast, and head and neck carcinomas), they highlight the potential relevance of adequate systemic exposure and thus dosing for achieving antitumor response in cetuximab pharmacotherapy. Further studies, however, are needed to clearly define an optimal systemic exposure range for cetuximab.

The pharmacokinetic parameter estimates of our final model are in line with a previous population analysis of cetuximab pharmacokinetics for regulatory purposes where a 2-compartment model with nonlinear elimination was also used.11,37 This analysis included 19 clinical studies in various cancer types. The similar results of the 2 analyses suggest that cetuximab pharmacokinetics are not different in patients with SCCHN compared with other cancer types. Our analysis did not identify an effect of concomitant chemotherapy, cisplatin/carboplatin, and 5-fluorouracil on cetuximab pharmacokinetics, which is in agreement with several earlier clinical trials.8,38 Furthermore, we could not detect differences in cetuximab pharmacokinetics for patients receiving cetuximab as first-line treatment during the recurrence or metastatic stage of SCCHN (study A) as compared with patients pretreated with at least 1 line of chemotherapy during this stage (study B). Although several of the tested covariates were not found to influence the pharmacokinetics of cetuximab (eg, gender, ethnicity, renal and hepatic function), it should be noted that most of the studied patients were male and Caucasian and had adequate hepatic and renal function. Therefore, the impact of these covariates on the pharmacokinetics of cetuximab remains to be elucidated.

In summary, we developed a population pharmacokinetic model for cetuximab that characterized the nonlinear pharmacokinetics of this monoclonal antibody. Ideal body weight and white blood cell count were identified as predictors for cetuximab clearance. The currently approved BSA-based dosing of cetuximab provides adequate exposure in most patients but may require adjustments in cases with extreme deviations of their body weight from their IBW.

The authors thank Dr Marc Gastonguay, Metrum Research Group, for his helpful comments regarding this analysis.

Financial disclosure: Dr Nathanael L. Dirks was supported by a fellowship from the American Foundation for Pharmaceutical Education. Drs Nolting and Kovar are employees of Merck KGaA. Dr Meibohm is a consultant for Merck KGaA.

REFERENCES


6. Sunada H, Magun BE, Mendelsohn J, MacLeod CL. Monoclonal antibody against epidermal growth factor receptor is internalized...


