Perspectives

The Importance of Pharmacokinetic Limited Sampling Models for Childhood Cancer Drug Development

J. Carl Panetta, Lisa C. Iacono, Peter C. Adamson, and Clinton F. Stewart


Abstract

Since the development of effective chemotherapy for children with cancer, it has been recognized that the response of children to apparently identical therapy, both in terms of efficacy and toxicity, can vary widely. Our understanding of the interindividual differences in drug metabolism and disposition as significant determinants of drug response continues to evolve. An increasing area of clinical investigation is focused on studies to gain a better understanding of the variability in critical drug metabolic and elimination pathways and how this variability translates into varied pharmacological effects. Analyzing how drug metabolism and elimination are affected by patient characteristics such as age, sex, race, organ function, drug interactions, and, perhaps most importantly, genetic polymorphisms, is now a routine component of drug development studies. Recent advances in analytical methodologies, computer hardware, and pharmacokinetic software have improved our ability to conduct studies of the disposition of anticancer drugs in larger, more representative pediatric populations. Along with advances in pharmacogenetics, the advances made in the conduct of pharmacokinetic studies in children with cancer have enabled establishment of sophisticated phenotype-genotype correlations, which may ultimately improve care. However, unique challenges and limitations remain that complicate the performance of pharmacokinetic studies in the child with cancer. This review addresses the need to perform pharmacokinetic studies throughout the drug development process in pediatric oncology patients, methods used to develop and validate limited sampling models, and selected examples of limited sampling models used in pharmacokinetic studies in children with cancer.

Introduction

Rapid advances in our knowledge of pharmacogenetics offer the future prospect of dose individualization based on genotypic profiles. A critical step in the development of pharmacogenetic dosing strategies is to link genotype to phenotype (drug exposure as defined by pharmacokinetic characteristics). During the drug development process it is essential that in addition to determination of the genotype of a patient, a thorough study of drug disposition be performed. Only through well-established genotype-phenotype correlations will successful development of pharmacogenetic-based dosing be realized.

Advances in pharmacokinetics can now allow for phenotyping of large populations of individuals. Technological advances in assay methodologies such as HPLC tandem mass spectrometry allow for sensitive and specific quantitation of drug in microvolume aliquots of plasma, an especially important requirement for pediatric pharmacokinetic studies. Modeling and computational advances allow for accurate determination of pharmacokinetic parameters using a limited number of specimens. Here, we present the current approaches to pharmacogenetic limited sampling methodologies and review the experience with these methods in pediatric cancer drug development.

Pharmacokinetics Studies in Childhood Cancer Patients

The initial evaluation of the disposition of an anticancer drug in children with cancer involves a detailed assessment of the processes of absorption, distribution, metabolism, and excretion. This provides the foundation for a pharmacologically rational treatment regimen. Drug disposition in children must also be interpreted in the context of developmental factors. The normal, dynamic changes that occur in organ function with development from neonate, infancy, and childhood through adolescence may significantly alter drug disposition. Changes in the functional capacity and enzymatic capabilities of major organs can substantially change drug clearance. Similarly, the changes in body composition (fat, protein, and water content) that occur during growth and development can directly influence drug distribution. Of note is that similar ideas should be considered in other patient populations such as the elderly, although many functional changes observed in the elderly are significantly different from in pediatrics.

Pharmacokinetic studies determine the primary parameters for the disposition of a drug, which include t1/2,2 volume of distribution, and CI. The classic two-stage approach (1) for determining the pharmacokinetic parameters of a population is to obtain multiple samples from each individual, usually serially.

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2 The abbreviations used are: t1/2, elimination half-life; CI, clearance; AUC, area under the curve; $C_{\text{max}}$, maximum concentration; MAP, maximum a posteriori probability; LSM, limited sampling model; TPT, topotecan; TMZ, temozolomide.

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at predetermined times, generally over at least three to four half-lives. The samples are analyzed for the concentration of parent drug and, when appropriate, metabolite, and a concentration-time curve is generated (Fig. 1). The $t_{1/2}$, volume of distribution, and CI are determined for each individual, and then in the second stage, population mean and SDs are obtained for the group studied, providing the basis for dosing regimens in children.

The two-stage approach is sampling intensive and usually performed in a limited number of children, typically 10–30 subjects. Fig. 1A depicts an example of a detailed sampling strategy that might be used for a pharmacokinetic evaluation of a compound with a terminal elimination half-life of 0.3 h. In this example, 12 blood samples were obtained over 8 h to define the plasma concentration-time profile. A compartmental model is then used to derive pharmacokinetic parameters. Parameter estimation techniques such as weighted nonlinear regression, maximum likelihood estimation, or MAP estimation, which are implemented in a variety of software programs such as Adapt II and WinNonLin, can yield individual pharmacokinetic parameters. From the primary compartmental parameters, secondary parameters, including CI or AUC, can be calculated.

Intuitively, the greater the frequency of sampling the more accurate the calculation of derived pharmacokinetic parameter estimates. The classic approach, however, does not account for sample times that may contain the most information about the parameter estimates. By applying more sophisticated methods that focus on the information content in individual samples, it is possible to substantially decrease the number of samples collected while obtaining a similar degree of accuracy in parameter estimation (Fig. 1B).

The basic two-stage approach described above is typical of the population pharmacokinetic studies performed in Phase I clinical trials in both adult and pediatric subjects. Investigators who design a pharmacokinetic study in children must address additional logistical issues (Table 1). Many of these are directly related to the additional safeguards afforded to children participating in research. A number of practical limitations challenge the performance of clinical pharmacokinetic studies in infants and small children. Fundamental to interpreting drug disposition in a patient is defining the plasma concentration-time curve (Fig. 1).

Important variables particularly relevant to pediatric pharmacokinetic studies are the volume of blood necessary for each sample and the number of samples required. Thus, the sensitivity and precision of the analytic methodology used to measure the drug in the matrix of interest (e.g., plasma, urine) are important aspects of pediatric pharmacokinetic study design. This stands in contrast to studies in adult subjects in whom blood volume or sampling frequency is rarely a primary consideration. For both pediatric and adult studies, however, cost is a relevant and important variable. The greater the number of samples obtained, the greater the consumption of clinical and laboratory resources. One increasingly used approach to maximize efficacy and accuracy while minimizing costs is to incorporate optimal and limited sampling strategies in the design of clinical pharmacokinetic evaluations. Furthermore, in both adults and pediatrics, the convenience of the sampling schedule must be considered. A sampling method that requires a sample in the late evening or one that requires a patient to make multiple trips to the clinic for samples may be optimal theoretically but is not convenient for both patient and staff and may discourage participation in the pharmacokinetic study. Thus, by adding constraints to the sampling times of the LSM, both a convenient and appropriate model can be derived.

In the emerging era of molecularly targeted therapies, the ability to explore pharmacodynamic relationships will be increasingly important in cancer drug development. Limited sampling methodologies will allow for pharmacokinetic-genetic-dynamic correlative studies to be performed throughout the clinical development process, starting in Phase I and potentially extending into Phase III. We will review the current approaches to developing LSMs, the experience in pediatric oncology to date with these methods and the future direction for the field.

![Fig. 1 Typical plasma concentration-time profile for a representative drug in a child.](image)

Table 1 Potential limitations to the performance of pharmacokinetic studies in infants and children

<table>
<thead>
<tr>
<th>Perception of ethical conflicts</th>
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<tbody>
<tr>
<td>Undue risks to child to perform pharmacokinetic study</td>
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<tr>
<td>Lack of understanding of scientific need for studies in children</td>
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<tr>
<td>Can not extrapolate pharmacokinetic data from adults to children</td>
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<tr>
<td>Analytical and laboratory based</td>
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<tr>
<td>Sensitivity and precision constraints</td>
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<tr>
<td>Small sample volume requirement</td>
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<td>Number of samples needed to accurately define drug disposition</td>
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</table>

**Small sample volume requirement**

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Approaches to Developing LSMs

LSMs have been used relatively frequently in adult oncology to study the pharmacokinetics of anticancer drugs (2–19) and, to a more limited extent, evaluated in pediatric studies (20–31). Approaches to LSMs can be grouped into two general categories: the linear regression approach and the D-optimality approach (for both individuals and populations) using Bayesian parameter estimation techniques.

Linear Regression Method

The use of multiple linear regression to correlate a pharmacokinetic end point such as Cl, AUC, or C_{\text{max}} (the dependent variable) to plasma concentrations at a limited number of sample times (the independent variable) has been common practice (27–31). The general approach is to extensively sample (typically \( n/1000 \)–\( n/8 \) samples/patient) from a training cohort of patients and use this information to generate the accurate estimate of the pharmacokinetic end point. Then, to determine the best limited sampling scheme of size \( k/n \), choose the subset of plasma concentration sample times such that the predicted pharmacokinetic end point is highly correlated to the actual pharmacokinetic end point (as determined by the complete sampling scheme). The resulting LSM is of the form:

\[
P_{\text{Kendpoint}} = A + \sum_{i=1}^{k} B_i C(t_i)
\]  

where \( P_{\text{Kendpoint}} \) is the pharmacokinetic parameter that is being estimated (e.g., AUC, Cl, and so forth), \( C(t_i) \) is the drug concentration at time \( t_i \), and \( A \) and \( B_i \) are the estimated parameters to the linear equation. Typically, stepwise regression techniques (32) are used to determine the best subset of sample times (usually defined as the subset of samples with the largest correlation coefficient \( r \) or smallest root mean sum of squares), which most accurately describe the pharmacokinetic end point. Once the regression equation is developed using the training set, the pharmacokinetic end point for future patients is estimated by solving the linear regression equation using the patient’s measured plasma concentrations at the appropriate times. One drawback of this method is that it is not flexible enough to handle cases where samples are taken at different times or dosing schemes differed from those used to generate the linear regression equation. It also assumes that the relation between the pharmacokinetic end point and concentration-time points is linear. Although for some end points such as AUC, the relation is linear, for others it may not be. For example, a typical nonlinear relation between drug concentration and Cl is:

\[
C(t) = \frac{D}{V} e^{-\frac{CL}{V} t} 
\]

and thus the relation between Cl and plasma concentration \( [C(t)] \) is:

\[
CL = \frac{V}{t} \ln\left(\frac{D}{V}\right) - \frac{V}{t} \ln(C(t))
\]

Therefore, the multiple linear regression approach may accurately estimate results for the average or typical patient but will generally give poor results for the patient who is not typical (e.g., a patient with organ dysfunction or a patient receiving a drug known to interact with the drug of interest). An example of this is observed using Monte Carlo-simulated data from TPT. A linear regression equation between three concentration time points and TPT clearance was developed using stepwise forward regression. As is depicted in Fig. 2, TPT clearance is poorly predicted by this method.

One method to account for the nonlinear nature of drug disposition is to transform the data, either by taking the logarithm of the pharmacokinetic end point or the logarithm of the concentrations. Fig. 3 demonstrates the results from a simulation analysis using TPT data after transformation of the data. Of note, however, is that the result is still not strictly linear.

These examples highlight the restrictions imposed by the linear regression method. First, it is only relevant for the specific...
sampling times and dose schemes used to generate the model. Second, many important pharmacokinetic parameters such as CI are not linearly related to drug concentrations. Thus, pharmacokineticists now frequently use more robust methods when developing an LSM.

**D-Optimality Method**

The main goal of an LSM is to estimate structural parameters of a model (e.g., pharmacokinetic or pharmacodynamic model) as accurately as possible. Thus, it is desirable to use a sampling method that reduces the SE estimate for the relevant parameters. Although LSM could be used to estimate parameters for a pharmacodynamic model, this review will focus on the application of LSM to pharmacokinetic models. All software packages used for compartmental modeling such as Adapt II (Biomedical Simulations, Los Angeles, CA) or WinNonLin (Pharsight Corporation, Mountain View, CA) are capable of estimating parameter variability. Once the compartmental model for a drug and population estimates of the pharmacokinetic parameters are determined, the SE of the pharmacokinetic parameters can be minimized. One of the most common methods is D-optimality (20, 33, 34), but a number of equally valid approaches, including A-, C-, E-, G-, and V-optimality, and Kullback-Leibler information can be used (35–37). The general idea of the D-optimality approach is to minimize, with respect to the concentration-time points, the SE estimates of the pharmacokinetic parameters. This is accomplished by minimizing the negative determinant of the Fisher information matrix (in which the inverse is the variance/covariance matrix of the parameter estimates). This approach generates the sample times that give the least amount of error in the estimate of the pharmacokinetic parameters. Fig. 4A is a graphical depiction of the negative determinant of the Fisher information matrix with respect to two sample times (the third sample time is fixed at 30 min). From this graph, we observe that along with the 30-min sample, a 2- and 7.5-h sample will generate the smallest value of the negative determinant of the Fisher information matrix. Fig. 4B shows these optimal samples on the corresponding concentration versus time plot. On the basis of this sampling scheme, the CI is estimated to have a coefficient of variation percentage of 7%. Several variations of D-optimal sampling should be considered. If the desired result is to obtain an accurate estimate of CI (or another single parameter), instead of minimizing the variance of all of the parameters in the pharmacokinetic model, only those parameters related to clearance are minimized, whereas the remainder is fixed at their average values. The D-optimal approach, however, requires the number of samples must be greater than or equal to the number of model parameters being optimized. For a two-compartment model that has four parameters, at least four samples would be required. To overcome this limitation, the D-optimality approach can be modified to use the Fisher Information Matrix for the MAP estimator (38), which accounts for the known distribution of the pharmacokinetic parameters. Thus allowing for the prior distribution of the pharmacokinetic parameters to influence the sampling scheme, fewer samples than model parameters can be used. The typical approach to implement these D-optimality methods is to first determine the appropriate compartmental model and estimate the population pharmacokinetic parameters using a training cohort of patients. Using this information, D-optimal sampling times are determined using a program like the SAMPLE subroutine in Adapt II or other methods. Then to estimate the pharmacokinetic parameters for each subject in the remaining cohort, which is sampled only at the optimal limited sampling times, a Bayesian parameter estimation method such as MAP, which is implemented in Adapt II, is used.

In many cases such as drugs with long half-lives, it is necessary to sample over longer periods (≥8–10 h) compared with the sampling method shown in Fig. 4. To avoid inconve-

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Fig. 3 Plot of actual versus predicted TPT lactone CI based upon multiple linear regression LSM, based upon log-transformed CI.
nient sampling times (e.g., late evening), constrained minimization may be added to D-optimality methods. Thus, one would minimize the negative determinant of the Fisher information matrix with respect to a set of predefined constraints. The D-optimality method implemented in Adapt allows one to constrain the samples to a single interval, whereas the minimization routines in Matlab allow inclusion of any number of constraints in the minimization problem. One example of a problem that required constrained minimization was with the drug oxaliplatin, which has a long terminal half-life (∼83 h; Ref. 39). To accurately estimate this terminal half-life, sampling was needed well past 8 h, although patients were only scheduled to return to the clinic once weekly. Thus, to maximize patient convenience, sampling times were constrained to the time interval 0–8 h or ∼1 week. We obtained the optimal sampling schedule of 0.5, 4, and 166 h after the end of infusion. To determine the validity of this constrained limited sampling method, we tested whether adding a sample at 24 h would significantly improve the accuracy of the drug CI, and little improvement was noted. Therefore, the LSM allowed patients to have their samples obtained on days 1 and 7 with acceptable accuracy.

Derivation of an LSM by this approach has several advantages. In contrast to the linear regression method, this method does not assume a linear relation between concentration-time points and the pharmacokinetic parameter(s). Therefore, it can estimate both parameters such as AUC and all other relevant pharmacokinetic parameters such as CI, volume, and half-life. Also, because the compartmental model is not specific to a particular dosage regimen or set of sample times, it will be accurate even if these differ from that of the training cohort.

Population Pharmacokinetic LSMs

LSMs can also be used to determine population pharmacokinetic parameters. This method is useful in cases where prior information on the pharmacokinetic parameters (e.g., the training cohort of patients) is not available or when the sole purpose of the study is to obtain population pharmacokinetic parameters. In this situation, sampling schemes can be more sophisticated in an effort to obtain accurate estimates of the population parameters. For example, if one is limited to three samples from each individual, it is not necessary to obtain the same sample times points from all individuals. Instead, one could sample half the

Fig. 4  A, contour plot of the determinant of the Fisher information matrix with respect to two of the three sample times (i.e., vertical and horizontal axes). The blue represents smaller values of the Fisher information matrix and red represents larger values. B, plot shows a concentration-time plot with D-optimal samples indicated.
**Table 2** Examples of LSM in pediatric oncology

<table>
<thead>
<tr>
<th>Drug</th>
<th>No. of patients</th>
<th>Dose/schedule</th>
<th>Summary of results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linear Regression</td>
<td>27</td>
<td>600 mg/m² over 4 days (37.5 mg/m² every 6 h for 4 days)</td>
<td>LSM for busulfan AUC = 122 + 0.97C_{0.5h} + 13.94C_{nh} (R² = 0.93). Validation used the same data as used in the model development.</td>
</tr>
<tr>
<td>Busulfan (47)</td>
<td>27</td>
<td>600 mg/m² over 4 days (37.5 mg/m² every 6 h for 4 days)</td>
<td>Three-sample (1, 1.5, and 6 h) and four-sample (1, 1.5, 2, and 6 h or 1, 1.5, 3, and 6 h). Three-sample method least different (mean percentage difference 7.5%) and highest correlation to the AUC_{Kaul} (r = 0.98) compared with published methods by Vassal and Schuler.</td>
</tr>
<tr>
<td>Busulfan (21)</td>
<td>9</td>
<td>40 mg/m² test dose via nasogastric tube</td>
<td>Validation used the same data as used in the model development. Authors report three-sample LSM by Chattergoon best correlation with the seven-sample AUC derived in this patient population.</td>
</tr>
<tr>
<td>Busulfan (23)</td>
<td>7</td>
<td>16 mg/kg (total dose) or 600 mg/m² (total dose) orally every 6 h over 4 days</td>
<td>Validation used the same data as used in the model development. Authors report three-sample LSM by Chattergoon best correlation with the seven-sample AUC derived in this patient population.</td>
</tr>
<tr>
<td>Piritrexim (27, 48)</td>
<td>17</td>
<td>70–145 mg/m² orally, every 12 h for 5 days</td>
<td>LSM defined by equation: $\text{Predicted AUC} = (3.19)C_{0.5h} + (6.54)C_{nh} + 1.11[\text{dose}(mg/m²/day)/140]$. Test in another group of patients (n = 15) who received full sampling and correlation between predicted and observed AUC was R = 0.98 (27).</td>
</tr>
<tr>
<td>Carboplatin (49)</td>
<td>23</td>
<td>200–1000 mg/m² over 60–90 min</td>
<td>Best LSM consisted of samples at 30 min after start of infusion and 60 min after the end infusion. The authors fit data from their LSM to a two-compartment model using Bayesian estimation to obtain estimates of carboplatin Cl and AUC. Overall determination of carboplatin AUC based upon an LSM approach was more accurate and less biased than the renal function approach.</td>
</tr>
<tr>
<td>Etoposide (20)</td>
<td>40</td>
<td>300 mg/m² over 2 h</td>
<td>LSM consisted of two samples at 1 and 12 h. The model was validated in a set of patient data. The mean bias 2.5% and accuracy 6.8%.</td>
</tr>
<tr>
<td>Oxaliplatin (39)</td>
<td>11</td>
<td>100–160 mg/m² over 2–4 h</td>
<td>LSM consisted of samples (plasma ultrafiltrate) at 2.5, 6, and 170 h after the end of the infusion. Coefficient of variation percentage for Cl = 14%.</td>
</tr>
<tr>
<td>TMZ (50)</td>
<td>30</td>
<td>145–200 mg/m²/day for 5 days</td>
<td>LSM consisted of 0.25, 1.25, and 6 h samples. Median bias and accuracy was &lt;1% and &lt;11%, respectively, for TMZ Cl, and &lt;2% and &lt;18%, respectively, for MTIC AUC.</td>
</tr>
<tr>
<td>TPT (51)</td>
<td>20</td>
<td>30-min infusion</td>
<td>LSM consisted of three plasma samples at 15 min, 1 h, and 6 h after the end of infusion. TPT lactone Cl determined in this study using the LSM with Bayesian estimation and D-optimality was similar to those previously published in other pediatric populations receiving continuous infusion TPT that used full plasma sampling sets.</td>
</tr>
<tr>
<td>Vincristine (52)</td>
<td>17</td>
<td>1.5 mg/m² i.v. bolus weekly for 4–8 weeks</td>
<td>LSM derived included pre, 10, 30, 90, 240, and either 600 or 1200 min after the start of infusion. The authors do not provide any additional information about this LSM in their article. They do not indicate whether or not it was validated. They were able to obtain vincristine clearance values that are comparable with those published in their previous study.</td>
</tr>
<tr>
<td>Other methods</td>
<td>6</td>
<td>0.8 mg/kg over 2 h four times daily for 4 days</td>
<td>LSM consisted of samples at 2.5 and 6 h Pharmacokinetic parameters (Cl/kg and V/kg) were estimated using a population approach. Monte Carlo simulations were performed. R = 0.970 using Pearson’s correlation test. The authors don’t perform an analysis to derive the plasma samples that they evaluate to create their LSM, possibly other time points might be more informative. The authors did not assess the accuracy and bias of the LSM predicted AUC compared with the AUC derived from the full data set.</td>
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patients at one set of sampling time points and the other half at an alternative set of sampling time points. This would give a better overall estimate of the population pharmacokinetics. This sampling approach has also been used successfully in single sample/subject toxicokinetic data (40). The goal is similar: define the plasma sampling times that yield the most accurate estimates of the population pharmacokinetic parameters along with accurate estimates of inter- and intrapatient variability. As detailed above, D-optimality can be used to determine appropriate sampling times. In this case, the negative determinant of the population Fisher information matrix is used (41, 42). Once the sampling scheme is defined, a mixed effects modeling program such as Nonmem (43) or WinNonMix (Pharsight Corporation) is used to estimate the population pharmacokinetic parameters.

Sample Size Considerations

Two general approaches have been proposed to estimate individual pharmacokinetic parameters with limited sampling: linear regression methods and Bayesian estimation methods. Both methods require the use of a prior set of pharmacokinetic information based on a complete sampling scheme to develop the predictive model. Two sampling issues must be considered when developing the training set: the number of subjects in the training set and the number and timing of samples obtained from each subject. If either of these issues is not optimal, then the LSM may be flawed.

A basic estimate of sample size needed to estimate the mean of a pharmacokinetic parameter with 100(1-α)% confidence and to have power β is given by equation 4 (44):

\[
 n = \frac{(z_{0.05} - z_\alpha)^2 \sigma^2}{\epsilon^2}
\]

where \( n \) is the estimate of the sample size, \( \sigma \) is the hypothesized SD, and \( \epsilon \) is the maximum error in the pharmacokinetic parameter.

As an example, consider TMZ Cl, which has an estimated mean and SD of 5.2 and 2.3 (liter/h/m^2), respectively (45). An estimate of the sample size needed to predict the population clearance within \( \epsilon = 1 \) (liter/h/m^2) (i.e., within 19% of the known clearance) and with \( \alpha = 0.05 \) (type I error) and \( \beta = 0.8 \) (type II error or power) is \( n = 42 \). If \( \epsilon \) is increased to 1.5 (liter/h/m^2; i.e., within 29% of the actual clearance), then the sample size needed will decrease to \( n = 19 \). In a similar manner, given a sample size of \( n = 30 \) the power to detect a 20% difference in TMZ clearance is \( \beta = 0.7 \), whereas the power to detect a 30% difference is TMZ clearance is \( \beta = 0.96 \). This is an important consideration in the situation where the LSM is derived from what could be thought of as a data-rich environment (e.g., many patients, full-sampling scheme).

Validation of LSM

Regardless of which method is used to derive the LSM, it is critical that the LSM be validated using an appropriate statistical approach. First, a suitable method for measuring the success of the LSM is needed. The most common and appropriate method is to determine the accuracy and bias of the LSM (46). One form of these measures is depicted in the following equations:

\[
\% \text{ accuracy} = \frac{\sum_{i=1}^{n} \left| \frac{x_{\text{actual}} - x_{\text{estimate}}}{x_{\text{actual}}} \right|}{n}
\]

\[
\% \text{ bias} = \frac{\sum_{i=1}^{n} \left( \frac{x_{\text{actual}} - x_{\text{estimate}}}{x_{\text{actual}}} \right)}{n}
\]

Although the correlation coefficient has also been used as a measure of accuracy and bias, it is not the preferable measure because it is likely that a highly correlated relation between the predictive and actual result may occur, although the best-fit line through the actual versus predicted parameter graph has a slope.

Table 2

<table>
<thead>
<tr>
<th>Drug</th>
<th>No. of patients</th>
<th>Dose/schedule</th>
<th>Summary of results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate (53)</td>
<td>20</td>
<td>Test dose</td>
<td>LSM consisted of samples at 0.5 and 6 h. The methotrexate Cl was estimated using a Bayesian estimator. Precision 11.2% and bias 1.9%. Bayesian prediction of MTX Cl using limited patient data permits dosage individualization of HD-MTX in routine situations with safety and performance comparable with that of the full sampling set.</td>
</tr>
<tr>
<td>Paclitaxel (25)</td>
<td>30</td>
<td>200–420 mg/m^2 over 24 h</td>
<td>LSM consisted of samples at 2, 5, and 8 h during the paclitaxel infusion. Mean error was &lt;23%. Did not provide details about the comparison between the simulated AUC values from LSM and full sampling. Could be considered an acceptable approach to developing a LSM (simulated data sets, fit model using Bayesian, compare LSM AUC to full set AUC); however, the use of the D-optimality approach would have been a more appropriate method for choosing time points.</td>
</tr>
</tbody>
</table>
significantly different from one (46). Thus, the predicted versus actual plot could be highly correlated but not predictive. Therefore, the measures defined in equation 5 are usually recommended.

Several methods have been proposed to validate an LSM. The most common method of validation is to compare the parameter estimate(s) from the training set using all available data (call this the correct parameters) to the estimate(s) of the parameters using the limited sampling subset of sampling times in the same group. From this, the accuracy and bias of the LSM can be estimated.

Another method to validate the LSM is by using Monte Carlo simulations. In particular, data are simulated based on the distribution of the pharmacokinetic parameters from a known population at the limited sampling times. The simulated limited sampling data are then fit to the pharmacokinetic model, and the predicted and actual pharmacokinetic parameters are compared using the measure of accuracy and bias described above. The advantage of the Monte Carlo-simulated data are that the actual pharmacokinetic parameters are known as opposed to merely having estimates of them as in the case of experimental data, and we are not limited to the size of a training set. Rather, we can simulate as many samples as necessary to obtain appropriate results.

Pediatric Oncology Experience with LSMs

LSMs have been developed for a number of currently used drugs for children with cancer as summarized in Table 2, but these studies represent only a small fraction of drugs used or in development for childhood cancer. Historically and because of its simplicity and ease of implementation, the linear regression method was the first approach used. More recently, D-optimality or related methods have been used. We describe in more detail a representative example using multiple linear regression by Mahmood (26) and one using D-optimality by Panetta et al. (20).

Selected Examples

Mahmood (26) developed a three-sample LSM for three generic drugs (only indicated as an antimigraine drug and two antiepileptic drugs) by the multiple linear regression approach using a training set of data from 10 adults. The methods used to develop the models were similar to those described earlier in this review. In particular, an LSM was determined for the AUC, $C_{\text{max}}$, and $\tau_{1/2}$ for each of the drugs. The models were then validated both in a set of adults ($n = 22–25$) and children ($n = 17–22$). A similar measure of accuracy and bias was used to determine the validity of these models as described in this review. Mahmood (26) concluded that for the three drugs considered, the LSM developed in the adult population adequately described the AUC and $C_{\text{max}}$ in the population of children. This study, although promising in relating adult pharmacokinetics to pediatric pharmacokinetics, has all of the limitations discussed earlier in this review. First, it is not surprising that the multiple linear regression model for the elimination half-life was not accurate because the relation between this and the concentrations is not linear. In a similar manner, the resulting model for $C_{\text{max}}$ should also be investigated more closely because this relation is also not linear. Next, the training set is relatively small and may not adequately describe the distribution of the pharmacokinetics for each of these drugs.

Another example is etoposide, an anticancer drug widely used in children with cancer for which relationships between pharmacokinetic parameters and outcome (toxicity and efficacy) have been studied. Although numerous etoposide clinical pharmacokinetic studies have been published, additional evaluation of etoposide disposition in children, especially in selected patient populations, may further optimize use of this drug and potentially allow for future therapeutic drug monitoring. Toward this goal, Panetta et al. (20) developed a LSM using a set of Monte Carlo-simulated data ($n = 1000$) based on the parameter distribution (mean and covariance matrix) for etoposide and etoposide catechol (dosed at 300 mg/m² by a 2-h i.v. infusion) measured in patients on a frontline institutional clinical trial for acute pediatric lymphocytic leukemia. Serial plasma samples (six to eight/patient) were obtained for up to 24 h after the infusion. A first-order two-compartment model for both the parent drug and metabolite was developed. Optimal sampling times were determined by D-optimality sampling using Bayesian methods. CI estimates were compared with the actual CIs from Monte Carlo-simulated data. To validate the LSM, predicted CI estimates were compared with CIs determined using all available plasma concentrations in clinical data from children with acute lymphoblastic leukemia. The accuracy and bias was 6.8 and 2.5%, respectively, confirming that the LSM yielded appropriate estimates of etoposide CI.

Conclusions and Recommendations

To define pharmacodynamic relationships during anticancer drug development, methods that allow for pharmacokinetic sampling in larger populations than traditionally studied during Phase I trials or in populations in whom frequent sampling is less feasible such as may exist in the very young child are needed. Advances in analytical capabilities in the laboratory and in computer software and hardware now allow for performance of more sophisticated clinical pharmacokinetic studies. LSMs will enhance our ability to define pharmacokinetic-pharmacodynamic relationships throughout the clinical drug development process. Applying LSM to study the pharmacokinetics of a drug in larger populations more representative of those in which the drug will ultimately be used, covering the spectrum of age, disease, and organ function variation, will further optimize cancer drug therapy. Population-based data integrated with Bayesian parameter estimation capitalize on sparse, fragmented data that when combined, accurately describes population-specific characteristics while concurrently allowing for estimation of an individual subject drug disposition parameters. These methods will take on increasing importance in the drug development process for children with cancer and decrease our reliance on extensive sampling in limited populations that form the basis for dosing recommendations in infants, children, and adolescents.

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