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A limited sampling method for estimation of the etoposide area under the curve*

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Abstract. A limited sampling method for estimation of the etoposide area under the curve (AUC) is presented. The method was developed and validated in 23 patients (42 pharmacokinetic studies) with small-cell lung cancer (SCLC), limited disease. The patients received 100 mg/m^2 etoposide as a 90-min intravenous infusion in combination with carboplatin, allowing for etoposide dose modification at a following course (25% increase or decrease) due to high or low nadir values for leukocytes or thrombocytes. Of the 42 pharmacokinetic studies, 27 were used in the model development and 15 were used in the model validation. Single regression analyses of the AUC versus the fitted concentrations for the model data set were performed at several time points. The analyses demonstrated high and essentially identical correlation coefficients in the interval between 2 and 21 h, with a maximal value of 0.96 being recorded at 4 h. Multiple regression analysis was then performed using fitted concentrations corresponding to 0.08–21 h. The best model for one sample was AUC = 1.01 × (dose level divided by 100 mg/m^2) + 799 × $C_{4\,h}$, that for two samples was AUC = 1.43 × (dose level divided by 100 mg/m^2) + 544 × $C_{4\,h}$ + 1756 × $C_{21\,h}$, and that for three samples was AUC = 0.07 × (dose level divided by 100 mg/m^2) + 110 × $C_{5\,min}$ + 474 × $C_{4\,h}$ + 1759 × $C_{21\,h}$. Not unexpectedly, the model validation revealed that the one-sample model was less precise than the two- or three-sample model [percentage of root mean squared error (RMSE%) = 11.6%, 7.1%, and 5.4%, respectively]. All models proved to be unbiased in the validation [percentage of mean predictive error (MPE%) ±SE = 4.2% ± 11.0%, 7.9% ± 6.1%, and 6.3% ± 5.3%, respectively]. The models were subsequently validated in 14 pharmacokinetic studies of patients with metastatic germ-cell tumours who were receiving combination chemotherapy with cisplatin and bleomycin plus 100 mg/m^2 etoposide as a 90-min infusion. The RMSE% was 13.4%, 10.8%, and 9.0% and the MPE% ± SE was −1.0% ± 11.9%, 1.7% ± 10.5%, and 2.7% ± 7.9% for the one-, two-, and three-sample models, respectively. The limited sampling methods presented herein may prove to be a most valuable tool for therapeutic drug monitoring in regimens in which etoposide is given in combination with carboplatin or with cisplatin and bleomycin.

Introduction

Therapeutic drug monitoring (TDM) has improved the efficacy and safety of treatment with a number of drugs (e.g., lithium, carbamazepine, aminoglycosides, digoxine). The current shortcomings of our knowledge about the relationship between dose and exposure on the one hand and between exposure and effect/toxicity on the other presents an argument in favour of close TDM of most cytostatic drugs that usually have a narrow therapeutic index. Nonetheless, TDM has found little use in clinical oncology. Stoller et al. [21] present a classic example of how cytostatic drug monitoring reduces treatment toxicity during high-dose methotrexate therapy in which leucovorin is given until the plasma methotrexate concentration drops below a certain threshold. Santini et al. [18] have obtained an improved complete response (CR) rate and less 5-fluorouracil (5-FU) toxicity upon dose adjustment based on the 5-FU plasma concentration in a study in which 5-FU was given in combination with cisplatin. In a phase I study of hexamethylene bisacetamide (HMBA), Conley et al. [4] have described a method for HMBA dose adaptation based on the relationship between the area under the plasma concentration versus time curve (AUC) and the relative decrease in thrombocytes.

Considerable interindividual differences are observed in the myelotoxic response to a standard dose (as measured in milligrams per square meter of body surface area) of etoposide. Studies have been carried out to examine the

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pharmacokinetics of etoposide and to correlate these parameters with antitumour or myelotoxic effects [1, 12, 23]. It has not yet been established as to which pharmacokinetic parameter best predicts etoposide toxicity (e.g., peak plasma level, AUC, duration of exposure) [13].

It is clear that further studies are warranted in this field so as to make cytostatic treatment more safe and effective. A major obstacle to such studies is that blood sampling for accurate determination of the AUC is quite time-consuming and costly. If patients receive etoposide as a constant venous infusion (CVI), the AUC can be estimated from the steady-state concentration, and this concentration seems to correlate well with the relative leukocyte decrease [12]. When etoposide is given as a short-term infusion, there is no such steady-state concentration and one has to draw many blood samples to measure an accurate AUC. Etoposide AUC determination in all patients receiving this drug is therefore hardly a feasible option.

A limited sampling method (LSM) would allow estimation of the AUC in many patients and would thus provide clinicians with a tool with which they could monitor the effect of drug exposure on both myelotoxicity and the antitumour effect.

LSMs have been developed for a small number of other cytostatics [5, 10, 14, 15, 17, 20]. Joel et al. [11] suggested an LSM for the estimation of etoposide pharmacokinetic parameters in etoposide single-agent therapy using three samples drawn at 1.5, 10, and 24 h after a 2-h infusion of 100 mg/m^2 etoposide. However, the drug is most often given in combination with other cytostatics. The present study was therefore performed to develop an LSM for etoposide given in combination with carboplatin or with cisplatin/bleomycin, an LSM that would be more suitable for practical purposes.

Patients and methods

The model was developed and validated in 23 previously untreated patients (10 men and 13 women) with small-cell lung cancer (SCLC), limited disease. Inclusion criteria were histologically or cytologically verified SCLC; measurable or evaluable disease; an age of <70 years; a glomerular filtration rate (GFR) of >30 ml/min, measured before the first and the third treatment as [^{51}Cr]-ethylenediaminetetraacetic acid (EDTA) clearance [2]; a WHO performance status of ≤ 3; and informed consent. Exclusion criteria were previous chemotherapy or radiation therapy or inadequate bone marrow function (a thrombocyte count of $<100 \times 10^9$/l or a leukocyte count of $<3 \times 10^9$/l before the first treatment.

Treatment. On day 1, the patients received a carboplatin dose calculated from the formula suggested by Calvert et al. [3]:

$$\text{dose in mg} = \text{target AUC} \times (\text{GFR} + 25),$$

where the target AUC is 5 mg min ml^{-1}. Carboplatin diluted in isotonic saline to a total volume of 300 ml was given as a 60-min infusion. Etoposide at a dose of 100 mg/m^2 per day diluted in isotonic saline to a total volume of 300 ml was given as 90-min infusions on days 1–3. The infusion rate was held constant with an IVAC infusion pump (model 281; IVAC Corporation, San Diego, Calif.). The treatment was repeated every 4 weeks.

Dose modification. The etoposide dose was reduced or increased by 25% at the following course if nadirs of leukocytes or thrombocytes were outside the range of $1.0-2.5 \times 10^9$/l or $30-125 \times 10^9$/l, respectively. A course was postponed for 1 week if the leukocyte or thrombocyte counts on the day of planned treatment were $<3.0 \times 10^9$/l or $<100 \times 10^9$/l, respectively.

Pharmacokinetic protocol. Blood sampling for etoposide pharmacokinetic analysis was performed on day 1 of the first and third chemotherapy courses, thus making 42 pharmacokinetic studies evaluable for analysis. Blood samples were drawn from an indwelling cannula in the arm opposite to the infusion site at the following time points: before etoposide infusion and at 5, 15, and 30 min as well as 1, 2, 3, 4, 6, 8, 10, and 21 h postinfusion.

Etoposide analysis. Determination of the etoposide plasma concentration was performed by high-performance liquid chromatography (HPLC). The analysis combined the methods described by El-Yazigi and Martin [6] and Werkhoven-Goewie et al. [22]. In brief, etoposide and the internal standard (teniposide) were extracted from plasma with chloroform. The organic phase was evaporated to dryness and the remnant was dissolved in 150 µl of the chromatographic eluent methanol/phosphate buffer (pH 3; 50/50, v/v). Then, 50 µl was chromatographed on a 12-cm reversed-phase (Nucleosil 300 5µ C18) column with an eluent flow rate of 1.2 ml/min. The compounds were detected by a fluorescence detector applying an excitation wavelength of 230 nm and an emmission wavelength of 328 nm. Retention times were 2.8 and 6.8 min for etoposide and the internal standard, respectively. The minimal detectable concentration using 0.1-ml samples was 25 ng/ml [coefficient of variation (CV) = 25%]. In the normal working range (0.1–20 µg/ml), the intra-day CV was <10%.

Pharmacokinetic analysis. The postinfusion total etoposide plasma concentration versus time curves were fitted to a biexponential equation using the computer program Graph Pad Inplot (GraphPAD Software, San Diego, Calif.), assuming a two-compartment model for the distribution and elimination of etoposide [9]:

$$c(t) = A' \times e^{-\alpha t} + B' \times e^{-\beta t}, \quad (1)$$

where $c(t)$ is the concentration at time t, A' and B' are concentration constants, and α and β are rate constants. As only postinfusion data were available in the present study, the AUCs from the beginning of the infusion to infinity were calculated from the fitted curve using the following equation [7]:

$$AUC_{0-\text{inf}} = \frac{A' \times T}{1 - \exp(-\alpha T)} + \frac{B' \times T}{1 - \exp(-\beta T)}, \quad (2)$$

where T is the infusion time. Etoposide plasma clearance was calculated as the dose in milligrams divided by the AUC.

Model development. Of the 42 pharmacokinetic studies, 27 (model data set, MDS) were used to develop an LSM. Fitted concentrations could be calculated from Eq. 1 at any time point. We correlated the fitted concentrations from numerous time points (ranging from 5 min to 22 h) with AUCs from the corresponding courses in the MDS to find the interval with the optimal single sampling time points.

To increase the precision of the method, multiple regression analyses (SOLO Statistical System, version 3.1, BMDP Statistical Software Inc., Los Angeles, Calif.) were performed to include another one or two sampling time points, if necessary. The etoposide AUC was the dependent variable and the fitted concentrations at different time points were the independent variables. A correction for dose modification, if any, was included in the model:

$$\text{AUC} = a \times (\text{dose level divided by 100 mg/m}^2) + b_1 \times x_1 + b_2 \times x_2 + b_3 \times x_3 \ldots \quad (3)$$

where $x_1 \ldots$ represents etoposide plasma concentrations at different hours.

Model validation. The models were validated in 15 pharmacokinetic studies from 15 patients (first validation data set, VDS1). Furthermore, we validated the models in 14 pharmacokinetic studies from 14 patients with metastatic germ-cell tumours (second validation data set, VDS2). These patients received 100 mg/m^2 etoposide over 90 min in combina-

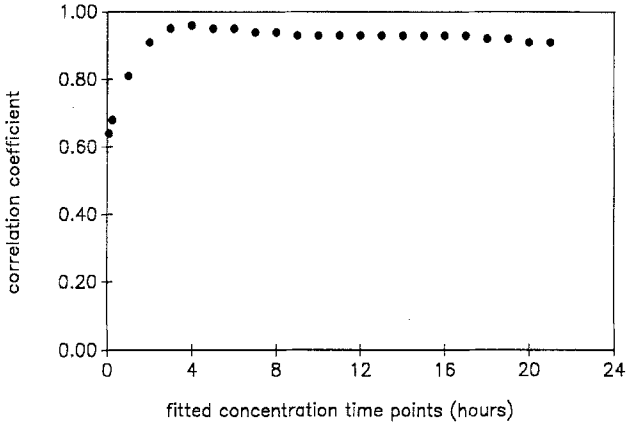

Fig. 1. Correlation coefficients for the etoposide AUC versus fitted etoposide concentrations at different hours in the MDS

tion with 20 mg/m^2 cisplatin over 30 min on days 1–5 and 15 mg/m^2 bleomycin on days 2, 9, and 16 as a short-term infusion. This treatment was repeated every 3 weeks, and the blood sampling for pharmacokinetic analysis was similar to that for the MDS and VDS1.

An estimate of the AUC was calculated from the concentrations measured at the selected time points. This estimate was correlated with the AUC determined from the fitted curve. The precision of the model was assessed by the percentage of root mean squared error (RMSE%), and bias was assessed by the percentage of mean predictive error (MPE% ± SE) [19].

Results

All patients received the same etoposide dose (in milligrams per square meter of body surface area) at the first course. The dose of the third course was modified (one decrease, five increases) according to the protocol in six patients from the MDS. The patients receiving the cisplatin/etoposide/bleomycin regimen (VDS2) required no dose modification. In Table 1, the main pharmacokinetic parameters for the MDS, VDS1, and VDS2 are shown.

Figure 1 depicts the regression coefficients in the MDS of fitted etoposide concentrations versus the AUC at different hours. High and essentially equivalent correlation coefficients were achieved for the interval ranging from 2 to 21 h postinfusion. The best correlation ($r = 0.96$) was achieved using the fitted concentration at 4 h postinfusion.

A multiple regression analysis included the 4-h sample followed by the 21-h and 5-min samples. The best one-, two-, and three-sample models, respectively, were as follows (note that the AUC is expressed in mg min ml^{-1} and the plasma concentrations are expressed in mg ml^{-1}): AUC = 1.01 × (dose level divided by 100 mg/m^2) + 799 × $C_{4\,h}$ ($r = 0.996$, $P = 0.00$), AUC = 1.43 × (dose level divided by 100 mg/m^2) + 544 × $C_{4\,h}$ + 1756 × $C_{21\,h}$ ($r = 0.999$, $P = 0.00$), and AUC = 0.07 × (dose level divided by 100 mg/m^2) + 110 × $C_{5\,min}$ + 474 × $C_{4\,h}$ + 1759 × $C_{21\,h}$ ($r = 1.000$, $P = 0.00$).

On *validation*, an increase in precision was achieved by adding a 21-h sample, and later a 5-min sample, to the 4-h sample (Table 2). Bias was modest in all three model validations. In Figs. 2 and 3, the actual versus the estimated AUCs for the three LSMs are shown for VDS1 and VDS2, respectively.

Discussion

A more than 3-fold variation was observed in the etoposide AUCs in course 1 (mean, 5.72 mg min ml^{-1}; range, 2.91–9.14 mg min ml^{-1}), during which all patients received the same etoposide dose in milligrams per square meter of body surface area. Thus, the AUC estimate based on one of the LSMs described herein yields a much better picture of the etoposide exposure than does the dose expressed in milligrams per square meter, even though there was a slight bias toward overestimation of the AUC with all three strategies (Table 2).

The validation of the models on the cisplatin/etoposide/bleomycin regimen (VDS2) shows an increase in RMSE% of 1.8%, 3.7%, and 3.6% in the one-, two-, and three-sample models, respectively. The MPE% did not rise, however; therefore, we can exclude the possibility that any systematic errors might have occurred when the models were applied to a combination regimen different from the one from which the model was developed.

Applying a *t*-test [testing dose-correction factor (a) = 0] to the MDS discloses that (a) contributes significantly to the AUC estimate with the one- and two-sample methods, whereas in the three-sample method, addition of the 5-min sample seems to make the correction for dose modification insignificant (*t* values: 9.50, 3.67, and 0.74, respectively;

Table 1. Main etoposide pharmacokinetic parameters for the model and validation data sets

	MDS, mean ± SD (range)	VDS1, mean ± SD (range)	VDS2, mean ± SD (range)
AUC (mg min ml^{-1})	5.68 ± 1.39 (3.25–9.14)	5.60 ± 1.58 (2.91–8.61)	5.86 ± 1.40 (4.22–8.91)
Plasma clearance (ml/min)	33.79 ± 8.68 (19.69–49.19)	33.47 ± 9.65 (19.70–58.50)	35.53 ± 8.17 (22.45–47.41)
$t_{1/2\beta}$ (min)	364 ± 120 (180–641)	332 ± 109 (138–527)	312 ± 101 (160–497)
$C_{5\,min}$ (mg/ml)	$16.8 \times 10^{-3} \pm 2.3 \times 10^{-3}$ (11.9×10^{-3}–22.2×10^{-3})	$15.3 \times 10^{-3} \pm 2.62 \times 10^{-3}$ (12.1×10^{-3}–20.1×10^{-3})	$16.6 \times 10^{-3} \pm 3.1 \times 10^{-3}$ (11.9×10^{-3}–24.7×10^{-3})
$C_{4\,h}$ (mg/ml)	$5.9 \times 10^{-3} \pm 1.7 \times 10^{-3}$ (3.0×10^{-3}–10×10^{-3})	$6.0 \times 10^{-3} \pm 1.5 \times 10^{-3}$ (2.8×10^{-3}–7.9×10^{-3})	$5.9 \times 10^{-3} \pm 1.3 \times 10^{-3}$ (4.0×10^{-3}–8.6×10^{-3})
$C_{21\,h}$ (mg/ml)	$0.7 \times 10^{-3} \pm 0.4 \times 10^{-3}$ (0–1.6×10^{-3})	$0.8 \times 10^{-3} \pm 0.5 \times 10^{-3}$ (0.02×10^{-3}–1.8×10^{-3})	$0.7 \times 10^{-3} \pm 0.4 \times 10^{-3}$ (0.02×10^{-3}–1.5×10^{-3})

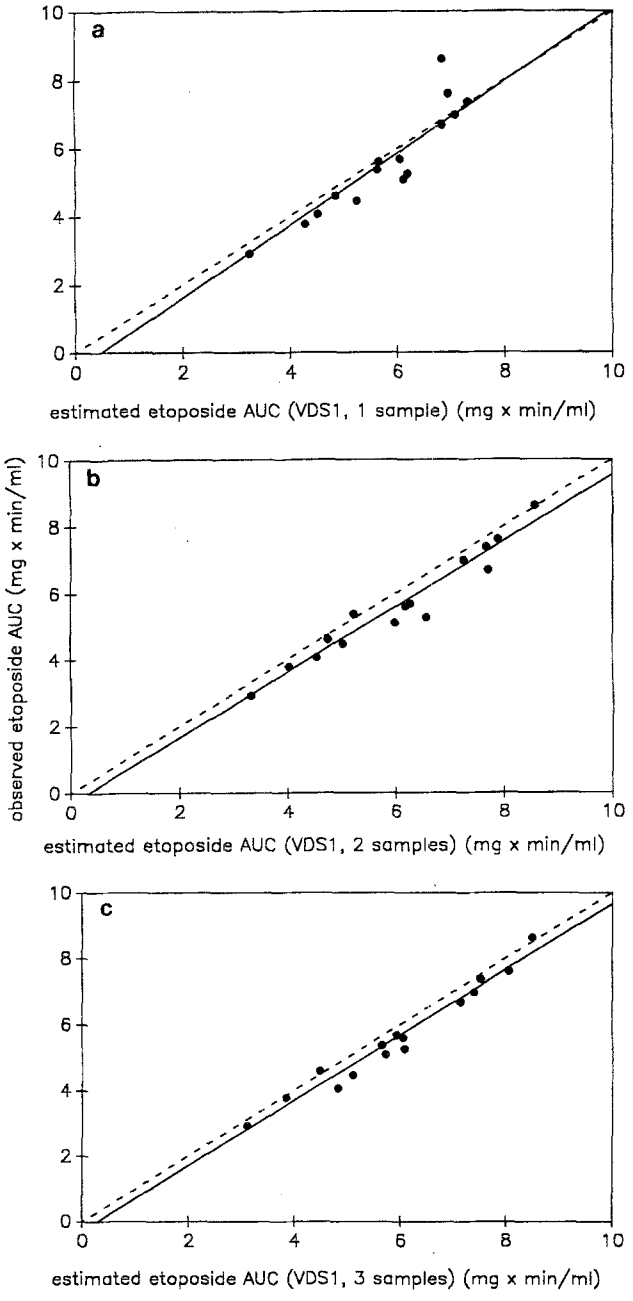

Fig. 2a–c. Observed etoposide AUCs versus AUCs estimated from 1 (**a**), 2 (**b**), or 3 plasma samples (**c**) in the first validation data set (*VDS1*). The line of unity (– – – –) and the linear regression line (———) are shown. The mean values ± SE for the slopes are 1.23 ± 0.15, 0.98 ± 0.07, and 1.00 ± 0.05, respectively, and those for the intercepts are –1.52 ± 0.87, –0.36 ± 0.43, and –0.38 ± 0.32, respectively; $r = 0.92$, 0.97, and 0.98, respectively

P values: <0.0001, 0.0012, and 0.47, respectively). This is not surprising, as a dose modification will be reflected especially in the etoposide concentrations of the early samples.

The application of the LSMs shown herein requires an infusion period of very close to 90 min and precise sampling times, especially with respect to the early samples in which the etoposide plasma concentration is rapidly decreasing.

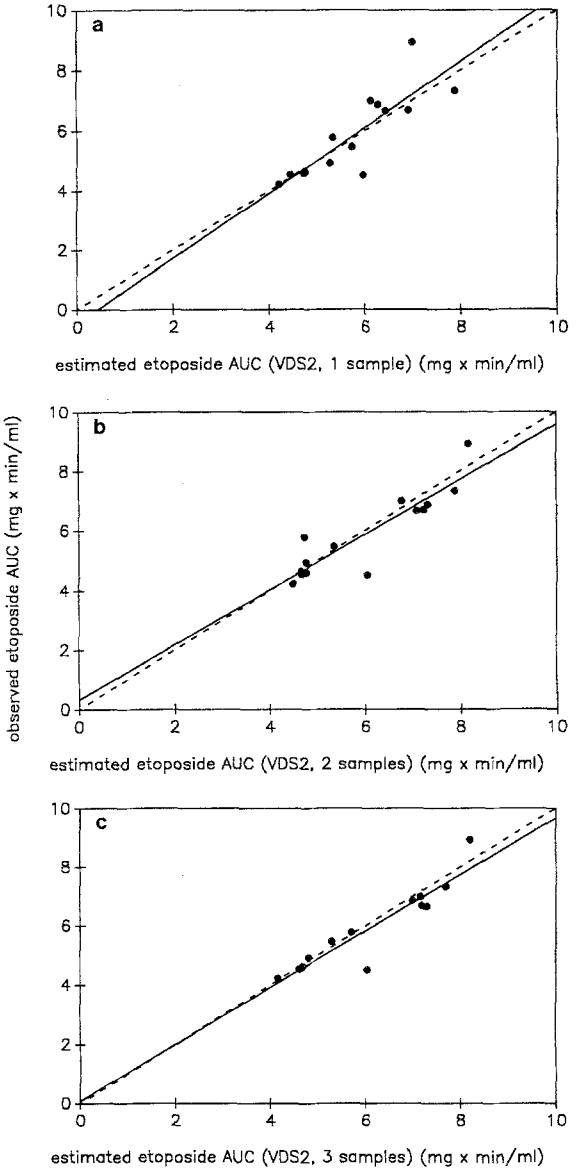

Fig. 3. Observed etoposide AUCs versus AUCs estimated from 1 (**a**), 2 (**b**), or 3 plasma samples (**c**) in the second validation data set (*VDS2*). The line of unity (– – – –) and the linear regression line (———) are shown. The mean values ± SE for the slopes are 1.10 ± 0.20, 0.92 ± 0.13, and 0.96 ± 0.11, respectively, and those for the intercepts are –0.48 ± 1.20, 0.32 ± 0.79, and 0.082 ± 0.66, respectively; $r = 0.84$, 0.90, and 0.93, respectively

Table 2. Validation of LSMs for estimation of the etoposide AUC

	Model validation		
	RMSE%	MPE% ± SE	*r*
Carboplatin/etoposide regimen (VDS1):			
4 h	11.6%	4.2% ± 11.0%	0.92
4 h/21 h	7.1%	7.9% ± 6.1%	0.97
5 min/4 h/21 h	5.4%	6.3% ± 5.3%	0.98
Cisplatin/etoposide/bleomycin regimen (VDS2):			
4 h	13.4%	–1.0% ± 11.9%	0.84
4 h/21 h	10.8%	1.7% ± 10.5%	0.90
5 min/4 h/21 h	9.0%	2.7% ± 7.9%	0.93

The pharmacokinetics of etoposide has been described as linear and dose-independent up to 800 mg/m^2 [8, 9]. The dose interval in this study was 150–250 mg/day (75–150 mg/m^2 daily). If the LSMs described herein are used in high-dose trials, we cannot exclude discrepancies due to altered pharmacokinetics.

Ratain et al. [16] have shown the feasibility of pharmacologically guided etoposide dosing when the drug is given as a continuous venous infusion over 72 h. In their study, the etoposide infusion rate was adjusted at 28 h according to the 24-h etoposide plasma concentration. The present study indicates that a similar dose adjustment on days 2 and 3 of a course can be performed if the plasma samples can be analyzed immediately. In this way, pharmacologically based dosing would also be possible for a short-term infusion. Furthermore, an AUC estimation based on an LSM would allow examination of the effect of drug exposure on both the myelotoxicity and the antitumour effect of the drug.

It is noteworthy that several LSMs yield acceptable levels of precision and bias. The use of LSMs in studies of population pharmacokinetics requires the choice of a method that is both accurate and practicable in daily routine. A 10-h sample such as that described in the work by Joel et al. [11] will almost invariably involve commitment beyond normal working hours, and an LSM using this sampling time would therefore not seem to be a particularly attractive choice in large-scale studies.

The present study shows that a three-sample approach is superior with respect to precision, whereas a single-sample approach is more convenient, disregarding the resulting increase in RMSE%. It can be debated as to which of the three methods is the better, but it should be borne in mind that a large-scale study demands the choice of a method that lends itself to daily routines. However, studies aimed at introducing TDM in daily routine therapy should be based on the best set of data. From this point of view, larger clinical studies using the two- or three-sample strategy are advocated.

We have previously described a method for estimation of the carboplatin AUC from two plasma samples drawn at 0.25 and 2.75 h after the termination of a 1-h carboplatin infusion [21]. If the LSMs for etoposide and carboplatin AUC estimation can be combined, it should be possible to evaluate the myelotoxic and antitumour effects of the combination of etoposide and carboplatin in a larger patient population.

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