Cancer Chemother Pharmacol (1994) 35: 179–181

SHORT COMMUNICATION

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Validation of a limited sampling model for carboplatin in a high-dose chemotherapy combination

Received: 9 May 1994 / Accepted: 10 June 1994

Abstract A limited sampling model for the estimation of the carboplatin area under the concentration versus time curve (AUC), as developed by Sørensen et al., was validated prospectively for the use in a high-dose combination chemotherapy schedule. The model allows an estimation of the AUC on the basis of only one timed plasma drug concentration, sampled at exactly 2.75 h after a 1-h carboplatin infusion. Pharmacokinetic curves were obtained from nine patients receiving carboplatin (400 mg/m^2 per day) combined with cyclophosphamide (1500 mg/m^2 per day), thiotepa (120 mg/m^2 per day), and mesna (3 g/day) for 4 consecutive days. Peripheral blood stem-cell transplantation (PBSCT) was performed 3 days later to restore hematopoiesis. Using this combination of high doses, the model proved to be unbiased (MPE –3.40%; SE, 1.22%) and highly precise [root mean squared prediction error (RMSE), 5.15%; SE, 0.17%] for estimation of the AUC during 4 consecutive days. The validated limited sampling model provides a starting point for future pharmacokinetic studies in a larger population of patients, which might lead to more insight into the relationships with the pharmacodynamic outcome of carboplatin and may help in achieving more rational dosing of patients on the basis of an AUC determination.

Key words Carboplatin · Limited sampling · Validation

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Introduction

Carboplatin [*cis*-diammino-1,1-cyclobutanedicarboxylato-platinum(II), CBDCA, JM8; NCS-241240] is a second-generation platinum-containing compound with activity against a wide variety of solid tumors [7]. Pharmacokinetic parameters, such as the area under the concentration versus time curve (AUC), may vary considerably among patients receiving the same carboplatin dose and schedule [3, 7]. It has been demonstrated that the AUC as compared with the dose is the parameter that correlates best with the extent of myelosuppression as well as with the antitumor effect [2, 3]. However, the exact relationships remain to be established, especially in very-high-dose schedules of carboplatin. Although the AUC is a useful pharmacokinetic measure of drug exposure, its exact quantification requires the withdrawal of multiple blood samples, usually at 10–15 different time points. The processing of these samples is inconvenient, time-consuming, and expensive. One approach to circumvent these problems is the use of a limited sampling model, which has recently been described for carboplatin [5]. This strategy allows an estimation of the AUC on the basis of only one timed plasma drug concentration, sampled at exactly 2.75 h after a 1-h carboplatin infusion [5]. There are some limitations in the use of limited sampling models, however. The model can be used only in the dose regimen that is an exact copy of the original regimen for which the model was developed [6]. Thus, concomitant administration of other drugs and the use of other infusion durations, higher doses, and other sampling sites may affect the predictive value of the model. In such cases the original model must be reevaluated and tested on a new validation-data set [6].

The objective of this study was to validate a limited sampling model for determination of the pharmacokinetics of high-dose carboplatin given for 4 consecutive days in combination with cyclophosphamide and thiotepa, with sampling being done through a Hickman catheter.

Patients and methods

Patient population

The nine patients from which complete pharmacokinetic curves were obtained participated in a phase II clinical trial utilizing a combination of three very-high-dose intensities of alkylating agents followed by peripheral blood stem-cell transplantation (PBSCT). The regimen has been described elsewhere [4]. In brief, it involves the administration of carboplatin (400 mg/m^2 per day) as a 1-h infusion followed by cyclophosphamide (1500 mg/m^2 per day) as a 1-h infusion and thiotepa (2 × 60 mg^2 per day) as 30-min infusions (the second infusion being given 12 h after the first), all given daily for 4 consecutive days. Mesna (500 mg) was given simultaneously six times daily for 6 consecutive days starting 1 h before the cyclophosphamide infusion. In four subjects (patients 2, 5, 6, and 7; see Table 1) the sequence of the infusions was reversed, with cyclophosphamide being given first, followed by thiotepa (first infusion) and carboplatin. Patients were randomized for the day (i.e., 1st, 2nd, 3rd, or 4th day) of pharmacokinetic sampling so as to exclude possible influences of preceding carboplatin courses. All infusions were given through a double-lumen Hickman catheter that had been inserted in a subclavian vein.

Pharmacokinetic studies

Blood samples were collected in heparinized tubes through the double-lumen Hickman catheter using the lumen that was not used for the administration of carboplatin. To avoid contamination of the sample with solution in this lumen, 10 ml of blood was withdrawn and discarded before the actual sample was taken. Samples were collected at 12 time points: immediately before, halfway through, and at the end of the infusion and at 0.25, 0.5, 1.5, 2.75, 5, 8, 12, 18, and 24 h after the end of the 60-min infusion. Plasma was obtained by immediate centrifugation (5 min; 1500 *g*) of the samples. Thereafter, plasma was transferred directly into an Amicon micropartition system with a YMT-30 membrane (Amicon Division, WR Grace & Co, Danvers, Mass., USA) and centrifuged for 10 min at 1500 *g*. The plasma ultrafiltrate was stored at –20° C until analysis.

Carboplatin was quantitated using a validated method based on Zeeman atomic absorption spectrometry. The lower limit of quantitation (LLQ) was 0.1 μ*M*, with the accuracy ranging from 93.9% (at the LLQ) to 103.3% and the within- and between-day precision varying from 1.5% to 10.2% (at the LLQ).

The exact AUC was calculated from the concentration-time curve by the trapezoidal method with extrapolation to infinity (C_{last}/λ_2, where C_{last} is the last measured concentration and λ_2 is the elimination rate constant). Linear regression analysis was performed on the terminal phase of the linear-log concentration-time curve to obtain λ_2. To account for the residual preinfusion carboplatin level (on days 2, 3, and 4), individual serum drug concentrations (C) at each sampling time (t) were corrected through the following equation:

$$C(t)_{corrected} = C(t)_{observed} - C(t)_{residual},$$

where $C(t)_{residual} = C(O) \times e^{-\lambda_2 \times t}$, whereby $C(O)$ is the preinfusion concentration at time zero.

Limited-sampling model validation

The exact AUCs determined from the concentration-time curves were compared with the estimated AUCs using the limited sampling model. This model is represented by the following equation [5]:

AUC (mg ml^{-1} min) = 0.52 (min) × [concentration at 2.75 h (mg/ml)] + 0.92 (mg ml^{-1} min).

The concentrations measured at 2.75 h were used for the prediction of the AUC with the model. The relative root mean squared prediction error (RMSE%), the relative mean prediction error (MPE%), and the relative standard error (SE%) were used to evaluate the performance of the model [6]. All statistical calculations were made using the computer program Quattro Pro (Quattro Pro package, version 4.00; Borland International, Scotts Valley, Calif., USA).

Table 1 AUC values observed and estimated for carboplatin in a combination chemotherapy regimen

Patient number	Day of course for sampling	Observed AUC[a] (mg ml^{-1} min)	Estimated AUC[b] (mg ml^{-1} min)
1	1	5.18	5.08
2	1	4.08	4.03
3	2	5.26	5.30
4	2	4.71	4.49
5	2	5.05	4.97
6	3	4.73	4.68
7	3	4.31	3.77
8	4	4.81	4.63
9	4	4.95	4.78

[a] AUC calculated by the trapezoidal rule with extrapolation to infinity using 12 measured plasma ultrafiltrate concentrations

[b] AUC calculated using the limited sampling model [5]: AUC = 0.52 × (concentration at 2.75 h) + 0.92

Results

Complete pharmacokinetics curves were obtained from nine patients. All patients had renal functions within the normal limits, with serum creatinine values ranging between 61 and 102 μ*M*. Two patients were sampled on the 1st day; three on the 2nd day; two on the 3rd day; and two on the last day of the course (Table 1). Thereafter, the AUCs estimated by the limited sampling model were compared with the actual values. The original %RMSE and %MPE values reported by Sørensen et al. [5] were 13.9% and –4.4% (±3.1%), respectively. In the present study, it appeared that the estimation of the carboplatin AUC remained precise, with the RMSE% being only 5.15% (±0.17%). The model was also unbiased, with the MPE% being –3.40% (±1.22%). Furthermore, the model appeared applicable on all days; correction for the residual carboplatin level from previous courses (days 2, 3, and 4) did not significantly influence the results – the relative magnitude of the residual AUC from the previous course as compared with the observed AUC was always <1%. The administration sequence of the cytotoxic agents, which was altered in patients 2, 5, 6, and 7, also did not affect the prediction of the model.

Discussion

The original limited sampling model reported by Sørensen et al. [5] was developed in ovarian cancer patients who received a 15-min infusion of cyclophosphamide (500 mg/m^2) followed by carboplatin (250, 375, or 500 mg/m^2) given as a 1-h infusion, which was repeated every month. This scenario contrasts with our group of patients, in whom a 3-fold higher dose intensity, a different duration of cyclophosphamide infusion, and a high dose of thiotepa were used. The courses were repeated every day for 4

consecutive days. Furthermore, a quite uncommon sampling site was used in the present study, which could possibly affect the measured concentration [1]. Since all these aspects may influence the accuracy, precision, and, thus, reliability of the limited sampling model, a prospective validation was performed.

The accuracy and imprecision values found were remarkably good, taken into consideration that the analytical procedure alone was associated with an imprecision ranging from 1.5% to 10.2% (at the LLQ). However, more importantly the model was tested in a patient population that was quite different from the original population.

The advantages of using this model are clear. The costs and efforts involved in the determination of the AUC are reduced substantially, as are the inconvenience for the medical staff and the patient and the possible infection hazard resulting from the sampling itself. Another concomitant advantage of the sampling procedure is that the sampling can be performed through a double-lumen Hickman catheter, eliminating the need for direct venipuncture.

In conclusion, it appears that neither the concomitant administration of high-dose chemotherapeutic agents, the altered administration sequence, nor the day or site of sampling affects the performance of the prediction. Furthermore, a correction for residual carboplatin levels from previous courses does not appear to be necessary with the present schedule. By using the validated limited sampling model, we hope to increase the feasibility of performing population pharmacokinetic studies. Eventually this may help us to dose patients more rationally on the basis of an AUC determination.

Acknowledgements We are grateful to the nursing staff of the 4A unit for their enthusiasm and the efforts that they put into the sampling procedure.

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