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A dosing scheme for carboplatin in adult cancer patients based upon pre-infusion renal function and platelet count

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The most important risk factors for the development of carboplatin-induced thrombocytopenia are total dose, glomerular filtration rate (GFR) and pre-infusion platelet count (P_0). Pharmacokinetic and toxicity data from 23 patients with ovarian or testicular cancer were combined with published values from four other centers and the relationships between plasma clearance of ultrafilterable platinum and GFR, and between percentage reduction in platelet count and area under the plasma platinum curve were determined. The scatter in the data was estimated and used in a Monte-Carlo computer simulation to derive the following five-level dosing scheme.

Total dose (mg)	GFR (ml/min)	P_0 (cells×10^3/μl)
900	>100	>200
750	80–100	>200
600	60–80	>200
450	30–60	>200
	>60	100–200
300	30–60	100–200

The scheme is based on 5% of patients incurring grade IV thrombocytopenia. Using this scheme, the majority of patients with ovarian or testicular cancer receiving carboplatin will be given an initial dose of 900 mg.

Key words: Cancer patients, carboplatin, dosing scheme, thrombocytopenia.

Introduction

Multiple infusions of *cis*-diammine-1,1-cyclo-butane-dicarboxylatoplatinum (carboplatin), at a dosing interval of 3–4 weeks, lead to tumor regression in patients with different types of malignancies.[1] The majority of clinical trials have used empirical doses for the initial cycle of chemotherapy. The most commonly used doses in clinical practice range from 300 to 400 mg/m^2 for first-line therapy and 240–270 mg/m^2 for patients who have had previous myelosuppressive therapy,[1–3] although doses as high as 1600 mg/m^2 have also been given.[4] All these studies have shown that the dose-limiting toxicity of this compound is myelosuppression, predominantly thrombocytopenia.

Egorin *et al.*[5,6] and van Echo *et al.*[7] correlated thrombocytopenia and renal function with area under the plasma platinum curve (AUC) and total body clearance. From these relationships equations were developed for calculating dose based upon renal function, body surface area, desired platelet nadir and prior chemotherapy. It is now clear that these equations should be viewed with caution.[8] A second scheme proposed that the total dose could be calculated to produce a desired AUC using only the patient's renal function.[9,10] However, since percentage reduction in platelet count (R) correlates with AUC[5] the use of a 'target' AUC (e.g. 4.5 mg.min/ml, as suggested for patients with testicular cancer[9,11]) implies an intended value of R. The value of R alone is insufficient to predict thrombocytopenia since the pre-infusion platelet count is also of importance. Moreover, both these dosing schemes do not take into account the considerable scatter in the experimental results.

In the present paper, pharmacokinetic and toxicity data are described for 23 patients with ovarian or testicular cancer, receiving carboplatin as a single agent or in combination with other cytotoxic drugs. The results are combined with published experimental values from four other centers.[4,5,9,12,13] Evaluation of the scatter in the experimental data enabled a Monte-Carlo model[14] to be used to develop a simple five-level dosing scheme based on the risk of a specified degree of thrombocytopenia. A dosing equation derived from the same experimental relationships, but neglecting the scatter, was shown to be inappropriate.

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Materials and methods

Ten patients of age 60 ± 9 years were diagnosed at laparatomy as having histologically proven advanced adenocarcinoma of the ovary. These patients had residual tumor after surgery and approximately 4 weeks later received the first course of carboplatin given as a single agent. Before therapy, the patients had liver function tests in the normal range, and creatinine clearances and platelet counts ranging from 45 to 111 ml/min and 147 to 712 × 10^3 cells/μl, respectively. Lyophilized carboplatin (Bristol-Myers, Middlesex, UK) in 150 mg vials, was reconstituted with 15 ml of sterile water and further diluted to a total volume of 1 l with a 5% solution of dextrose. Patients received a carboplatin dose ranging from 360 to 400 mg/m^2 administered by constant rate i.v. infusion over 30 min (patients 1–10, Table 1). No hydration or diuretics were given. The anti-emetic regime consisted of 500 mg i.v. methyl prednisolone immediately prior to cytotoxic drug therapy and 250 mg 3 h later.

The remaining 13 patients of age 31 ± 10 years had metastatic teratoma of the testis. Before therapy, liver function tests were in the normal range, and creatinine clearances and platelet counts ranged from 91 to 238 ml/min and 187 to 630 × 10^3 cells/μl, respectively. At 3 week intervals, these patients received 30 min i.v. infusions of carboplatin at doses ranging from 375 to 560 mg/m^2 with no concomitant hydration or diuretics (patients 11–23, Table 1). Etopside (250 mg) was given immediately after carboplatin and at 24 and 48 h. Bleomycin (30 mg) was administered i.m. on days 3, 8 and 15 post-carboplatin infusion. The anti-emetic regime consisted of chlorpromazine (25 mg) as required. Platelet counts were determined weekly, and the nadirs occurred between 14 and 21 days after carboplatin administration.

Plasma was collected at the end of carboplatin infusion, and at 0.5, 1, 2, 4, 6, 8, 12, 24 and 48 h. Aliquots of plasma were immediately ultrafiltered at 4°C using Amicon CF25 conical filters (Amicon Ltd, Gloucester, UK). The filtrates were stored at −20°C before platinum analysis using atomic absorption spectrophotometry.[15]

The AUC for ultrafilterable platinum was calculated by summing the area during infusion by the trapezoidal method and integrating the post-infusion area to infinity after fitting a biexponential decay curve: $C=Ae^{-\alpha t}+Be^{-\beta t}$, where C is concentration and t is time. Plasma clearance (Cl_p) was

Table 1. Plasma platinum AUC, kidney function (GFR) and percent platelet reduction (*R*) in 23 patients: 1–10 ovarian cancer; 11–23, testicular cancer [also given are the body surface area (BSA) and administered carboplatin dose (*D*)]

Patient	BSA (m^2)	*D* (mg)	AUC ($\mu g.h/ml^{-1}$)	GFR (ml/min)	*R* (%)
1	1.60	640	43.8	45	37
2	1.60	576	34.2	62	79
3	1.70	680	19.4	63	44
4	1.50	600	31.4	69	36
5	1.54	600	29.8	78	78
6	1.50	600	17.4	80	33
7	1.55	600	33.9	84	21
8	1.74	694	41.8	80	36
9	1.70	680	26.6	102	49
10	1.50	600	32.0	111	80
11	1.77	900	29.4	109	17
12	1.81	750	67.6	120	86
13	1.68	900	46.4	135	43
14	1.88	750	35.2	146	86
15	1.99	900	30.5	141	12
16	2.18	900	48.0	114	64
17	1.98	750	39.4	238	38
18	1.77	900	47.5	91	74
19	2.10	900	30.2	158	62
20	1.80	900	17.8	161	—
21	2.00	750	36.4	153	69
22	1.80	750	27.3	156	—
23	1.61	900	27.0	170	86

determined by dividing the total dose (D) by AUC. A Monte-Carlo model was developed to simulate the scatter in the relationships between pharmacokinetic parameters, kidney function and platelet reduction. Details of the model are given in the Appendix.

Results and discussion

Table 1 shows the pre-infusion glomerular filtration rate (GFR; as measured by creatinine clearance) and the percentage reduction in platelet count (R) in 23 patients receiving carboplatin. At the end of infusion, the plasma platinum concentration ranged from 7.7 to 22.8 mg/ml and then fell biexponentially ($t_{1/2\alpha}$ 0.4–1.6 h, $t_{1/2\beta}$ 1.7–29.2 h) over 48 h. The calculated AUC, also shown in Table 1, ranged from 17.4 to 67.6 μg.h/ml and R ranged from 0 to 86%.

The values of AUC and R, combined with those published previously,[4,5] were fitted by a sigmoidal curve (Figure 1a) of the form:

$$R = \frac{100\text{AUC}^m}{K + \text{AUC}^m} \quad (1)$$

using a least squares fit. Equation (1) was first transformed to a linear form as shown by equation (6) (Appendix). Figure 1(b) shows the relationship between Cl_p and GFR for the 23 patients combined with published values derived from 52 patients.[5,9,12,13] The data were fitted by a power law of the form:

$$Cl_p = \frac{D}{\text{AUC}} = a\text{GFR}^n + b \quad (2)$$

Again a least squares fit was used after transformation of equation (2) to linear form (equation 5, Appendix). Exponential and linear functions were

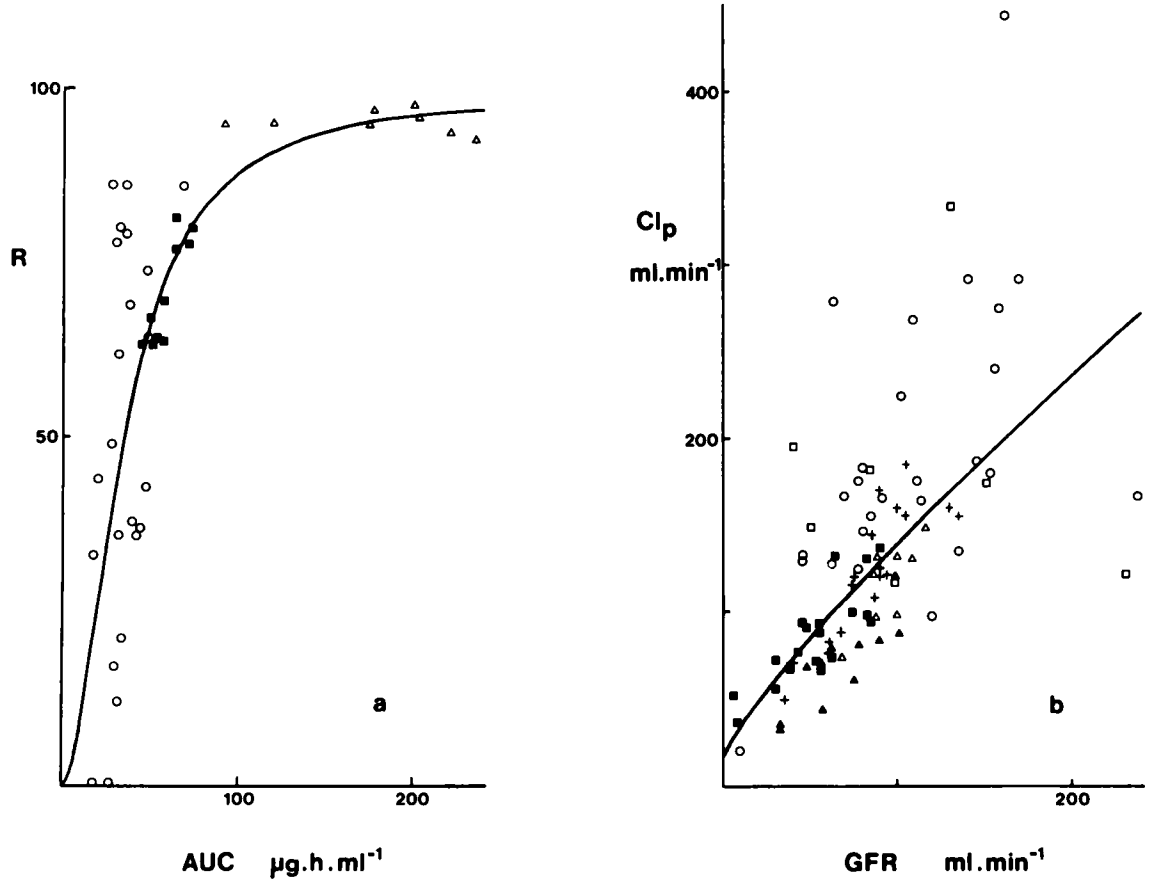

Figure 1. (a) Relationship between percentage reduction in platelet count (R) and area under the plasma platinum curve (AUC) in 40 patients. The constants in the fitted sigmoidal curve are $m = 1.85$ and $K = 675$. (b) Relationship between plasma clearance (Cl_p) and glomerular filtration rate (GFR) in 75 patients. The constants in the fitted power law are $a = 2.46$, $n = 0.847$ and $b = 17.0$. Present study, ○; Egorin *et al.*,[5] ■; Calvert *et al.*,[9] +; Newell *et al.*,[4] △; Reece *et al.*,[12] □; Gaver *et al.*,[13] ▲.

also fitted to the data but gave lower correlation coefficients (0.670, 0.618) than the power law (0.741).

In addition to the value of R, the importance of the pre-infusion platelet count (P_0) in the development of thrombocytopenia is seen from the definition of R:

$$R = \frac{P_0 - P_1}{P_0} \times 100 \qquad (3)$$

where P_1 is the platelet nadir. For a high P_0 value, e.g. 500×10^3 cells/μl, and a P_1 of 25×10^3 cells/μl (Grade IV thrombocytopenia), equation (3) shows that R = 95%. However, if P_0 is 100×10^3 cells/μl, a value of R of only 75% produces the same P_1.

Combining equations (1)–(3) leads to a dosing equation relating D, GFR, P_0 and P_1:

$$D = 9.64(\mathrm{GFR}^{0.847} + 6.90)(P_0/P_1)^{0.541} \qquad (4)$$

Thus, from a patient's pre-infusion platelet count and GFR, theoretically a dose could be calculated for a clinically acceptable platelet nadir.

A major problem with the type of dosing formula given by equation (4) and the other proposed dosing equations for carboplatin[5,9] is that they convey no information about the likely scatter in the values of P_1 for a given P_0, GFR and D. When a dose is calculated from equation (4) to achieve an acceptable value of P_1, some patients may still incur unacceptably low values of P_1 due to statistical fluctuations. With the Monte-Carlo model it is possible to estimate the number of patients at risk from a specified degree of thrombocytopenia. For a given P_0, GFR and D a distribution of values of P_1, as shown in Figure 2, is obtained. In this example, the dosing formula (equation 4) predicts a P_1 of 100×10^3 cells/μl for all patients, whereas the model predicts that in 20% of patients, P_1 will be below 50×10^3 cells/μl and in 6% of patients P_1 will be below 25×10^3 cells/μl.

For given values of P_0 and GFR, the model was used to determine the value of D such that $P_1 < 25 \times 10^3$ cells/μl in 5% of patients, taking this as a reasonable level of risk. The results are given in Figure 3. It is possible to simplify this information for clinical use by dividing P_0 and GFR into ranges, a single dose level applying to each range. The dosing scheme is given in Table 2 and represents the administration of 2, 3, 4, 5 or 6 vials (150 mg) of carboplatin.

A preliminary study was carried out for 20 patients with testicular cancer and GFR values (EDTA clearance) above 100 ml/min who received a total of 58 cycles of carboplatin in combination with etopside and bleomycin. All patients had P_0 values above 200×10^3 cells/μl. Nine patients (29 cycles) were given 750 mg carboplatin per cycle; the mean

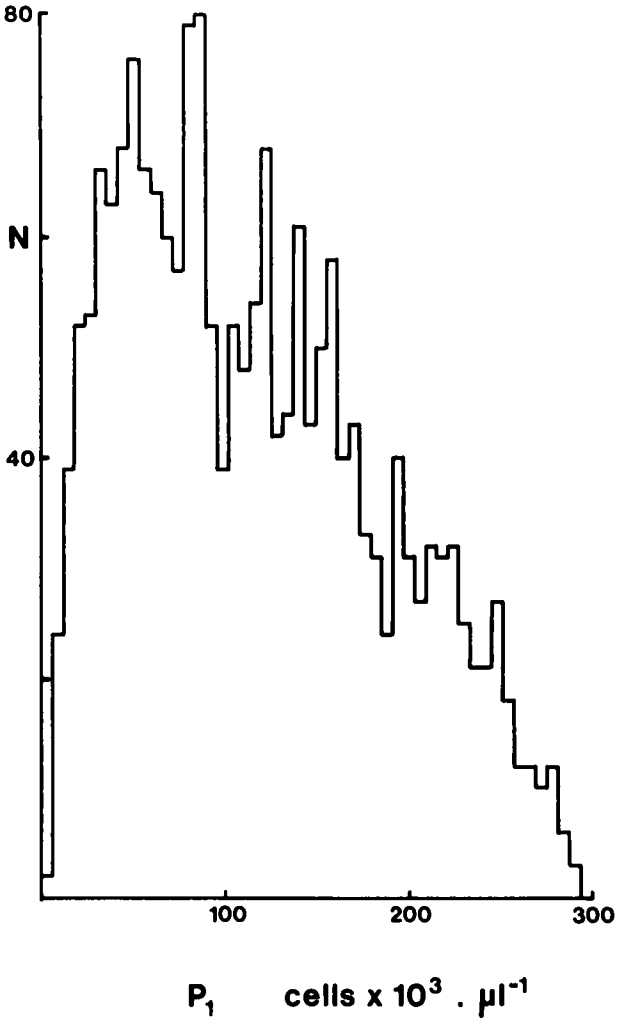

Figure 2. Distribution of platelet nadir (P_1) obtained by Monte-Carlo simulation of 2000 patients with $P_0 = 300 \times 10^3$ cells/μl, GFR = 50 ml/min and D = 482 mg. P_1 is divided into intervals of 6000 cells/μl and N is the number of patients in each interval.

Table 2. Proposed dosing scheme for carboplatin

Total dose (mg)	Pre-infusion GFR (ml/min)	Pre-infusion platelet count (cells × 10^3/μl)
900	>100	>200
750	80–100	>200
600	60–80	>200
450	30–60	>200
	>60	100–200
300	30–60	100–200

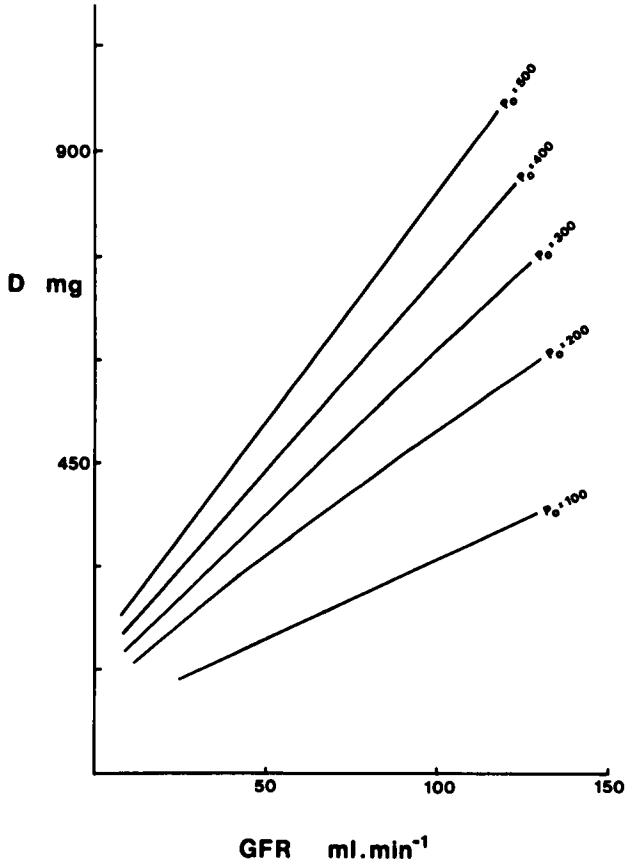

Figure 3. Monte-Carlo estimates of carboplatin dose (*D*) for different values of GFR and P_0 (cells$\times 10^3$/μl) when 5% of patients have $P_1 < 25 \times 10^3$ cells/μl.

(±SD) GFR and P_1 were 138 ± 21 ml/min (range 100–169 ml/min) and 126 ± 61$\times 10^3$ cells/ml (range 29–286$\times 10^3$ cells/μl). The remaining 11 patients (29 cycles) received 900 mg carboplatin per cycle; the mean GFR and P_1 were 184 ± 33 ml/min (range 149–261 ml/min) and 82 ± 42$\times 10^3$ cells/μl (range 17–211$\times 10^3$ cells/μl). Grade IV thrombocytopenia was observed in none of the patients at the lower dose level but occurred in two patients at the higher dose. The combined incidence of grade III and grade IV thrombocytopenia was significantly different ($p = 0.04$) at the two dose levels, being 6 and 30% of the cycles at 750 and 900 mg respectively. These results suggest that the higher carboplatin dose of 900 mg, as specified by the new dosing scheme, should be the initial dose given to teratoma patients having GFR > 100 ml/min and $P_0 > 200 \times 10^3$ cells/μl. In patients where platelet reduction is low (e.g. $P_1 > 100 \times 10^3$ cells/μl) after the first cycle of carboplatin, it may be possible to escalate the dose to 1050 mg. In contrast, using the dosing formula of Newell *et al.*[11] multiple doses of only 563 or 788 mg would have been given for GFR values of 100 or 150 ml/min, respectively.

Conclusion

Given the large scatter in the experimental data presented in this paper, it is clearly inappropriate to use a dosing equation derived only from the fitted experimental relationships to predict carboplatin-induced thrombocytopenia. Although statistical analysis using the Monte-Carlo method has recently been applied in biochemistry to estimate uncertainties in parameter values for protein–ligand binding,[16] to our knowledge this is the first report of its use for drug dosage development in clinical pharmacology. The proposed scheme is based upon the major risk factors for the development of thrombocytopenia, i.e. the patient's pre-infusion platelet count and kidney function.[8,17] The value of the scheme in pediatric oncology should also be investigated.

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Appendix

Following the linear least squares fitting of $\log R/(100-R)$ versus log AUC from which the constants m and K were determined for equation (1), the standard deviation (σ) of the data about the regression line was estimated from an analysis of variance and assumed to be constant over the entire range of AUC. The value obtained was $\sigma = 0.437$. A χ^2 test of the deviations from the regression line against a Gaussian distribution with the same σ showed no significant difference ($p = 0.09$). A similar procedure was carried out for equation (2) giving $\sigma = 0.212$ and $p = 0.4$, again indicating that the scatter could be regarded as Gaussian.

The Monte-Carlo computer model incorporates the linearized forms of equations (1) and (2) plus scatter terms derived from the computer's internal pseudo-random number generator:

$$\log(Cl_p - b) = n \log \mathrm{GFR} + \log a + E_1 \qquad (5)$$

$$\log \frac{R}{100 - R} = m \log \mathrm{AUC} - \log K + E_2 \qquad (6)$$

where the scatter terms E_1 and E_2 have Gaussian distributions, zero means and standard deviations equal to the experimentally determined values above. In the model, a hypothetical patient can be simulated starting with values of GFR and D. A value of AUC is determined from equation (5). Substituting this into equation (6) with a given P_0 leads to a value for P_1. By simulating a large number of patients a complete distribution of values of P_1 is obtained.