

# Evaluation of Equations for Carboplatin Dosage

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## ABSTRACT

A retrospective chart review was conducted to evaluate a set of equations which use a patient's creatinine clearance (CrCl), body surface area, pretreatment platelet count, desired platelet nadir, and prior chemotherapy to calculate an appropriate carboplatin dose, and to determine if estimates of CrCl could be used in the dosing equations.

The published equations were rearranged to predict the change of platelet count for the carboplatin dose the patient received. Correlations between observed and predicted change in platelet counts were determined.

Forty-nine patients received carboplatin (84 courses of therapy) at the Saskatoon Cancer Centre. In 36% of the 84 courses of therapy, the predicted change in platelet count ( $\Delta PC_{pred}$ ) was within  $\pm 25 \times 10^9$  platelets/L of the observed change ( $\Delta PC_{obs}$ ). Thrombocytopenia (platelets  $< 100 \times 10^9/L$ ) was predicted in 16 of the 25 cases (64%) in which it occurred.  $\Delta PC_{pred}$  was highly correlated with  $\Delta PC_{obs}$  both for the first courses of carboplatin the 49 patients received (slope=0.98,  $r=0.80$ ) and for all 84 courses of carboplatin (slope=1.10,  $r=0.79$ ).

Estimated CrCl values and Egorin et al's equations could be useful in predicting carboplatin dosage. However, additional research should be conducted to compare the validity of the equations for sequential courses of carboplatin and for patients with and without prior cisplatin therapy.

**Key Words:** antineoplastic, carboplatin, creatinine, dosage, platelet, renal

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## RÉSUMÉ

Une analyse rétrospective de dossiers a été menée afin d'évaluer une série d'équations basées sur la clairance de la créatinine (ClCr), la surface corporelle, la numération plaquettaire pré-traitement, le nadir plaquettaire désiré et une chimiothérapie antérieure chez un patient donné, et qui ont été utilisées pour calculer la dose de carboplatine appropriée et déterminer si les valeurs prédites de la ClCr pouvaient être utilisées dans les équations posologiques.

Les équations, qui ont fait l'objet d'une publication, ont été réarrangées de manière à prédire toute variation du nombre de plaquettes liée à la dose de carboplatine que le patient a reçue. On a pu ainsi établir des corrélations entre les variations observées et prédites du nombre de plaquettes.

Au Saskatoon Cancer Centre, 49 patients ont reçu au total 84 traitements au carboplatine. Dans 36 % des 84 traitements, les variations prédites du nombre de plaquettes ( $\$NP_{pré}$ ) étaient inférieures à  $\pm 25 \times 10^9$  plaquettes/L des variations observées ( $\$NP_{obs}$ ). Une thrombocytopenie (nbre de plaquettes  $< 100 \times 10^9/L$ ) avait été prédite dans 16 des 25 cas (64 %) de thrombocytopenie observés. Il y avait une forte corrélation entre les  $\$NP_{pré}$  et les  $\$NP_{obs}$  à la fois pour la première série de traitements au carboplatine administrée aux 49 patients (pente=0,98,  $r=0,80$ ) et pour l'ensemble des 84 traitements au carboplatine (pente=1,10,  $r=0,79$ ).

On a conclu que les valeurs prédites de la ClCr et les équations de Egorin et ses collègues pouvaient être utiles pour déterminer la dose de carboplatine adéquate. Cependant, des recherches additionnelles sont nécessaires afin de comparer la validité des équations dans les traitements séquentiels au carboplatine et chez les patients qui ont déjà reçu ou non un traitement au cisplatine.

**Mots Clés :** antinéoplasique, carboplatine, créatinine, posologie, plaquettes, rénal.

## INTRODUCTION

Cisplatin, the first platinum compound developed for cancer treatment,<sup>1</sup> has a broad spectrum of activity and has become recognized as highly effective for treatment of testicular, lung, ovarian, and head and neck cancers.<sup>2</sup> However, severe side effects, including intense nausea and vomiting, nephrotoxicity, ototoxicity, neurotoxicity and myelosuppression, limit

the dose of cisplatin which may be given to a patient.

Carboplatin, a cisplatin analogue with comparable anticancer activity to cisplatin,<sup>3,4</sup> is very convenient to administer on an outpatient basis relative to cisplatin, causes significantly less nephrotoxicity, neurotoxicity and ototoxicity than cisplatin, and appears to be less emetogenic than cisplatin.<sup>3-5</sup> However, at therapeutic

doses, carboplatin causes more myelosuppression, particularly thrombocytopenia, than cisplatin.<sup>3-5</sup> This myelosuppression is often the side effect which limits the dose of carboplatin that can be administered.<sup>3-6</sup>

The likelihood of treatment failure because cancer cells develop resistance to chemotherapy may be reduced by giving maximally tolerated

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doses of chemotherapy.<sup>7,8</sup> To achieve a balance between tumor reduction and myelosuppression, the dosage of carboplatin is often escalated, or reduced, based on platelet and neutrophil count nadirs and tumor response.<sup>5</sup>

Because clearance of carboplatin is directly related to glomerular filtration rate (GFR),<sup>9,10</sup> dosing has also been based on renal function.<sup>4,5,11,12,13</sup> The formula of Calvert et al for calculating carboplatin dosage is based on GFR, but does not take into account patient specific variables such as body surface area (BSA) and platelet counts, and also requires a value for plasma concentrations of carboplatin (i.e., a value for the area under the plasma concentration-time curve of ultrafilterable platinum).<sup>12</sup> Egorin et al developed equations to calculate optimal carboplatin doses using a patient's creatinine clearance (CrCl, mL/min), BSA (m<sup>2</sup>), pretreatment platelet count, desired platelet nadir, and history of prior chemotherapy.<sup>13</sup>

This information is readily available in most clinical situations and therefore should be easier to use for carboplatin dosage adjustment than the Calvert et al method.

Egorin et al used data from 22 patients to develop these dosing equations for carboplatin and later prospectively evaluated the equations

(23 patients, 38 courses of therapy).<sup>14</sup> CrCl used in the equations was the mean of two 24-hour CrCl values measured within one week prior to treatment.

The purpose of this study was to examine the accuracy of Egorin's dosing equations and to determine if use of a serum creatinine-based estimate of CrCl could be used in the equations. We were also interested in comparing the accuracy of the equations for first and subsequent courses of carboplatin therapy, for patients with low and high CrCl, and for patients with previous cisplatin therapy.

## METHODS

Patients receiving carboplatin between April 1986 and April 1991 were retrospectively reviewed for: age, sex, diagnosis, height, weight, BSA (m<sup>2</sup>), serum creatinine (SCr), baseline platelet count, platelet nadir (lowest count from once weekly bloodwork between treatments), and concurrent chemotherapy. CrCl (mL/min) was estimated using the Cockcroft-Gault formula.<sup>15</sup>

By algebraically rearranging the Egorin et al formulas,<sup>13,14</sup> the change in platelet count was "predicted" ( $\Delta PC_{pred}$ ) for the dose the patient had received.

The definition for "heavily pretreated patients" was that of Egorin et al, i.e., patients who had received

mitomycin C; a nitrosurea; combination chemotherapy with doxorubicin, cyclophosphamide and cisplatin; chemotherapy with five or more different agents; or radiotherapy  $\geq 4500$  rads to a single port (20cm x 20cm) or more than one field of therapy.<sup>14</sup>

Accuracy of the formula for carboplatin dosage was evaluated by comparing the patient's  $\Delta PC_{pred}$  to the observed change in platelet count ( $\Delta PC_{obs}$ ). To provide a comparison to the data analysis used by Egorin et al, the association between  $\Delta PC_{pred}$  and  $\Delta PC_{obs}$  was examined by linear regression. T-tests were used to compare means of continuous variables and the Chi-square test to compare categorical variables between patient subgroups (SPSS-X<sup>®</sup> Data Analysis System, Release 3.0). Results were considered to be statistically significant at  $p \leq 0.05$ .

## RESULTS

Eighty-four courses of carboplatin therapy, involving 49 patients, were reviewed during the study period (Table I). Carboplatin was administered with: cyclophosphamide (46 courses); etoposide (18 courses); epirubicin (six courses); 5-fluorouracil (one course); and two or more other antineoplastics (six courses). In seven courses of therapy, patients did not receive any other antineoplastic agent.

For previously untreated patients:

$$\text{Dosage (mg/m}^2\text{)} = (0.091) \frac{(\text{CrCl})}{\text{BSA}} \left[ \frac{\text{pretreatment platelet count} - \text{desired platelet nadir} \times 100}{\text{pretreatment platelet count}} \right] + 86$$

For patients heavily pretreated with myelosuppressive agents:

$$\text{Dosage (mg/m}^2\text{)} = (0.091) \frac{(\text{CrCl})}{\text{BSA}} \left\{ \left[ \frac{\text{pretreatment platelet count} - \text{desired platelet nadir} \times 100}{\text{pretreatment platelet count}} \right] - 17 \right\} + 86$$

$$\text{For heavily pretreated patients: } \Delta PC_{pred} = \left[ \frac{(\text{dose} - 86)}{0.091} \left( \frac{\text{BSA}}{\text{CrCl}} \right) + 17 \right] \cdot \frac{(\text{pretreatment platelet count})}{100}$$

$$\text{For other patients: } \Delta PC_{pred} = \frac{(\text{dose} - 86)}{0.091} \left( \frac{\text{BSA}}{\text{CrCl}} \right) \cdot \frac{(\text{pretreatment platelet count})}{100}$$

In 49 courses of therapy (58%), carboplatin was administered for the first time to a patient; 24 courses (29%) were second carboplatin doses; 11 courses (13%) were the third doses administered to individual patients. Thrombocytopenia (platelets  $<100 \times 10^9/L$ ) occurred in 25 of 84 courses (30%) of carboplatin administration. Four patients had a platelet count less than  $25 \times 10^9/L$ . There were no cases of overt bleeding episodes in these 25 courses of thrombocytopenia, however, two patients exhibited petechiae and six (including the four with platelets  $<25 \times 10^9/L$ ) received infusions of platelets and/or packed red blood cells.

The  $\Delta PC_{pred}$  for all 84 courses of carboplatin administration was highly correlated with the  $\Delta PC_{obs}$  (slope=1.10,  $r=0.79$ ; Table II). The correlation was similar for the 49 first courses of carboplatin (slope=0.98,  $r=0.80$ ; Table II). Although the correlation between  $\Delta PC_{pred}$  and  $\Delta PC_{obs}$  was statistically significant for the 39 second courses of therapy, the slope was higher than one (1.41) and the y-intercept was negative. The correlation for the 11 third courses of therapy was not statistically significant ( $r=0.55$ ,  $p=0.08$ ).

The accuracy of the equations can also be illustrated by examining the differences between  $\Delta PC_{pred}$  and  $\Delta PC_{obs}$ . In 17 of 84 courses (20%), the equations overestimated  $\Delta PC_{obs}$  by greater than  $25 \times 10^9/L$  and in 37 of 84 courses (44%), the equations underestimated  $\Delta PC_{obs}$  by greater than  $25 \times 10^9/L$ . Equations were considered "accurate" ( $\Delta PC_{pred}$  within  $\pm 25 \times 10^9/L$  of  $\Delta PC_{obs}$ ) in 36% of all 84 courses; 35% of the 49 first courses of therapy, 29% of second courses and 55% of third courses (Table III). To simplify subsequent presentation of results for different patient subgroups, only data from the 49 first courses of therapy are discussed in the following sections.

A total of 10 patients were classified as heavily pretreated; one of these

Table I: Study Population

Patient Characteristics	
Age (y)	59.0 $\pm$ 12.9
Weight (kg)	69.1 $\pm$ 16.9
BSA (m <sup>2</sup> )	1.75 $\pm$ 0.23
CrCl (mL/min) <sup>a</sup>	83.4 $\pm$ 32.1
Pretreatment platelet count (cells $\times 10^9/L$ )	389 $\pm$ 181
<b>Diagnosis</b>	
Ovarian cancer	27 (57 courses of therapy)
Lung cancer	17 (21 courses of therapy)
Other <sup>b</sup>	5 (6 courses of therapy)
<b>Drug Therapy</b>	
Heavily pretreated	10
Prior cisplatin therapy	8 (5 heavily pretreated)
Initial carboplatin dose (mg/m <sup>2</sup> )	289 mg $\pm$ 47
<b>Total</b>	
	49 (84 courses total)
	39 females/10 males

<sup>a</sup> as estimated by Cockcroft-Gault formula from serum creatinine concentration

<sup>b</sup> one case each of oral pharyngeal cancer, multiple brain tumours, glioblastoma, thymoma and unknown primary cancer

<sup>c</sup> values reported for age, weight, BSA, CrCl, platelet count and dose are mean  $\pm$  standard deviation

Table II: Correlation of Observed and Predicted Change in Platelet Counts

SUBGROUP	N	SLOPE	INTERCEPT <sup>a</sup>	r	p-value
<b>All courses of therapy</b>	84	1.10	14.12	0.79	<0.0001
First courses	49	0.98	31.64	0.80	<0.0001
Second courses	24	1.41	-42.80	0.84	<0.0001
Third courses	11	1.12	24.36	0.55	0.08
<b>Heavily pretreated<sup>b</sup></b>					
Yes	10	0.71	57.47	0.65	0.04
No	39	0.99	32.81	0.81	<0.0001
<b>Prior Cisplatin therapy<sup>b</sup></b>					
Yes	8	1.10	-21.04	0.94	0.0007
No	41	0.95	43.28	0.79	<0.0001
<b>Creatinine clearance<sup>b</sup></b>					
<60 mL/min	12	1.07	-49.24	0.97	<0.0001
$\geq 60$ mL/min	37	1.14	18.53	0.69	<0.0001

<sup>a</sup> values entered as platelets  $\times 10^9/L$

<sup>b</sup> includes only first courses of therapy

patients received two courses of carboplatin. Patients who had been heavily pretreated had significantly lower pretreatment platelet counts (268 versus  $420 \times 10^9/L$ ,  $p=0.02$ ) and nadir platelet counts (97 versus  $166 \times 10^9/L$ ,  $p=0.05$ ) than those patients not heavily pretreated. The change in platelet count after the first course of carboplatin was also smaller (170 versus  $255 \times 10^9/L$ ,  $p=0.05$ ), perhaps because of the slightly lower doses received by those patients who had previously been heavily pretreated with other chemotherapy (150 versus  $174 \text{ mg/m}^2$ ,  $p=0.1$ ). For patients

classified as heavily pretreated, the correlation between  $\Delta PC_{pred}$  and  $\Delta PC_{obs}$  for the first course of therapy was lower (slope=0.71,  $r=0.65$ ; 10 courses of therapy), than for patients not heavily pretreated (slope=0.99,  $r=0.81$ ; 39 courses of therapy). However, in five of 10 cases (50%) of heavy pretreatment,  $\Delta PC_{pred}$  was within  $\pm 25 \times 10^9/L$  of  $\Delta PC_{obs}$ , whereas only 12 of 39 predictions (31%) were "accurate" for patients who had not been heavily pretreated (Table III). The difference was not statistically significant, but the power of the comparison was limited by the small

number of patients who had been heavily pretreated.

Eight of the 49 patients had received prior therapy with cisplatin; five of those eight were classified as heavily pretreated. Patients with prior cisplatin therapy had a tendency to a lower CrCl (72 versus 86 mL/min,  $p=0.06$ ) and lower pretreatment platelet counts (285 versus 409  $\times 10^9/L$ ,  $p=0.07$ ). The correlation coefficient was slightly higher for those patients who had previously received cisplatin than those who had not, but in one case the y-intercept was negative and in the other it was positive (Table II). In five of eight patients who had previously received cisplatin (62.5%),

$\Delta PC_{pred}$  was within  $\pm 25 \times 10^9/L$  of  $\Delta PC_{obs}$ , whereas only 12 of 41 predictions (29%) were “accurate” for patients who had not previously received cisplatin. Thus,  $\Delta PC_{obs}$  was underestimated in only 12.5% of cases with prior cisplatin therapy, but 49% of cases without ( $p=0.1$ ) (Table III).

In 12 patients (25%) receiving carboplatin for the first time, CrCl was  $<60 mL/min$ . Only two of these 12 patients had received heavy pretreatment and only one, previous cisplatin therapy. For the 12 patients with low CrCl, the correlation between  $\Delta PC_{pred}$  and  $\Delta PC_{obs}$  was significant ( $r=0.97$ ), with a slope close to one (1.07) (Table II). The correlation

coefficient in the 37 patients with  $CrCl \geq 60 mL/min$  was smaller ( $r=0.69$ ) and the slope slightly higher (1.14). For 33 and 35% of patients, with low and high CrCl respectively,  $\Delta PC_{pred}$  was within  $\pm 25 \times 10^9/L$  of  $\Delta PC_{obs}$ .  $\Delta PC_{obs}$  exceeded  $\Delta PC_{pred}$  by  $>25 \times 10^9/L$  in 49% of patients with  $CrCl \geq 60 mL/min$ , but only 25% of patients with  $CrCl < 60 mL/min$  (Table III).

**DISCUSSION**

Egorin et al based their prediction equations on linear relationships between clearance of ultrafilterable platinum (from carboplatin) and CrCl ( $r=0.82$ , 19 data points) and between area under curve (AUC for ultrafilterable platinum) and percentage change in platelet count.<sup>13</sup> Correlation of AUC with change in platelet count was better than with platelet nadirs. The regression lines for a plot of percentage change in platelet count versus AUC were parallel for patients who were heavily pretreated ( $r=0.73$ , 5 data points) and those without excessive prior chemotherapy ( $r=0.89$ , 10 data points). The y-intercepts, however, differed by 17, indicating that patients who had been heavily pretreated experienced a 17% greater reduction in platelet count for a given AUC. Thus the dosing equation for heavily pretreated patients incorporated a factor of “17” to reduce the dose required to achieve a given percent change in platelet count.<sup>13</sup>

When prospectively evaluating their own dosing equations for

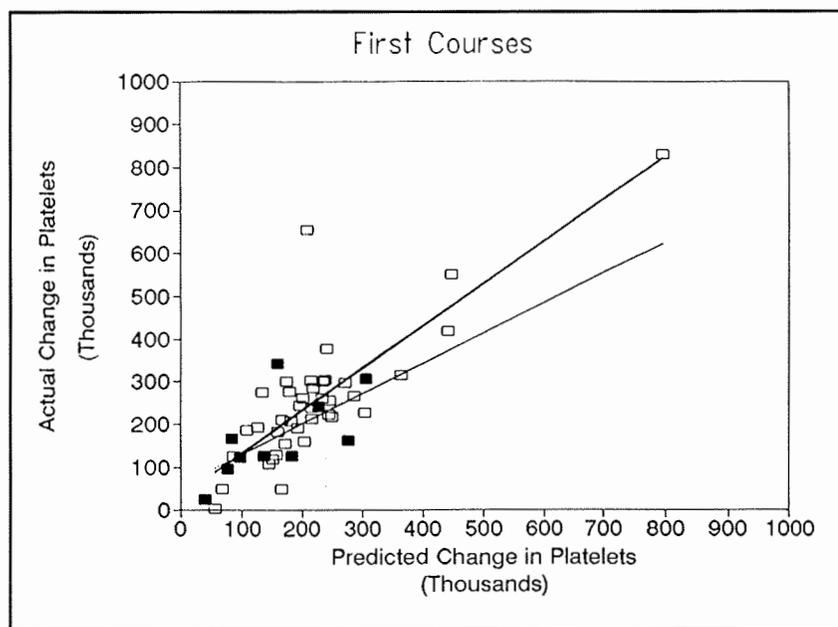


Figure 1: Correlation of Observed and Predicted Changes in Platelet Counts for First Courses of Carboplatin: without heavy pretreatment, □-□, heavy solid line; with heavy pretreatment, ■-■, solid line (Parameters of regression lines as indicated in Table II).

Table III: Differences between Observed and Predicted Change in Platelet Counts

Difference $\Delta PC_{obs} - \Delta PC_{pred}$ (Platelets $\times 10^9/L$ )	Course of Therapy			Heavy Pretreatment <sup>a</sup>		Prior Cisplatin <sup>a</sup>		CrCl <sup>a</sup> mL/min	
	First	Second	Third	Yes	No	Yes	No	<60	$\geq 60$
<-25,000	22%	21%	9%	20%	23%	25%	22%	42%	16%
-25,000 to 25,000	35%	29%	55%	50%	31%	62.5%	29%	33%	35%
>25,000	43%	50%	36%	30%	46%	12.5%	49%	25%	49%
Total (N)	49	24	11	10	39	8	41	12	37

<sup>a</sup> only first courses of therapy included

carboplatin, Egorin et al reported a high correlation (slope=0.96,  $r=0.94$ ) between observed and predicted changes in platelet counts for 38 courses of therapy in 23 patients.<sup>14</sup> In our retrospective analysis of 84 courses of carboplatin administration in 49 patients,  $\Delta PC_{pred}$  correlated well with  $\Delta PC_{obs}$  (slope=1.10,  $r=0.79$ ; Table III). When just the first courses of carboplatin were evaluated, the relationship more closely approximated the line of identity, but the correlation (slope=0.98,  $r=0.80$ ) was similar to that observed for all 84 courses of therapy (Table III). The correlation for the third courses of therapy was not statistically significant. Predictions underestimated the actual change in 43% of the first courses of therapy (49), 50% of the second courses (35) and 36% of the third courses (11). Egorin et al did not distinguish between first and subsequent courses of therapy in their study,<sup>14</sup> therefore, data for the same patients entered the correlation more than once if patients received more than one course of therapy.

The correlation between  $\Delta PC_{pred}$  and  $\Delta PC_{obs}$  was the poorest for the 10 patients who were classified as heavily pretreated (slope=0.71,  $r=0.65$ ). However, despite the relatively poor correlation, in 50% of the cases in our study,  $\Delta PC_{pred}$  was within  $\pm 25 \times 10^9/L$  of the observed value. Egorin et al reported a much stronger correlation of observed and predicted change in platelets in 11 patients classified as heavily pretreated (slope=1.13,  $r=0.97$ ).<sup>14</sup> Despite the use of only 5 points to establish the relationship between percentage change in platelets and AUC of carboplatin for patients who had been heavily pretreated,<sup>13</sup> correlations are surprisingly good.

Approximately 60-80% of carboplatin is excreted in the urine in the first 24 hours after injection<sup>10</sup> and clearance of carboplatin-derived platinum is highly dependent on renal function.<sup>13</sup> As a result, the manu-

facturer recommends that empiric dosage adjustments be made when  $CrCl < 60 mL/min$ .<sup>16</sup> This dosage adjustment is important in controlling the thrombocytopenia experienced by patients receiving carboplatin. Accuracy of any dosage prediction equations is particularly important for patients with low  $CrCl$ . For patients who had a larger change in platelets than predicted by the equations, doses calculated from the equations described by Egorin et al<sup>14</sup> may hold an increased risk of bleeding. For the first course of therapy in the 12 patients in our study with  $CrCl < 60 mL/min$ ,  $\Delta PC_{obs}$  and  $\Delta PC_{pred}$  were highly correlated (slope=1.07,  $r=0.97$ ). Egorin et al also reported a good correlation in 10 heavily pretreated patients in their study with  $CrCl < 60 mL/min$  (slope=1.17,  $r=0.99$ ).<sup>14</sup> In the current study, only two of the 12 patients with a  $CrCl < 60 mL/min$  had been heavily pretreated and only three had a  $\Delta PC_{obs}$  which exceeded the  $\Delta PC_{pred}$  by  $> 25 \times 10^9/L$ . Therefore, in nine of 12 cases with low renal function, the equations predicted a reasonably safe dose of carboplatin with respect to changes in platelet count. For the 37 patients with a  $CrCl \geq 60 mL/min$ , the correlation between  $\Delta PC_{obs}$  and  $\Delta PC_{pred}$  was not as high (slope=1.14,  $r=0.69$ ; Table II), but the intercept was closer to zero.

Both in the development of the dosing equations<sup>13</sup> and in their validation,<sup>14</sup> Egorin et al did not distinguish between patients who had or had not received prior therapy with cisplatin. Although Egorin et al designated the dosing equations for "previously untreated" and "heavily pretreated" patients, the more appropriate terminology is that contained in the 1984 article; i.e., patients with and without "extensive prior chemotherapy".<sup>13</sup> Only two of the 22 patients in the first study and one of 23 patients in the second study had received no prior chemotherapy. However, these authors did not indicate how many of the patients had

received cisplatin before carboplatin. Our results suggest a trend that the dosing equations may perform differently depending on whether or not patients had prior cisplatin therapy. While the correlation of  $\Delta PC_{obs}$  and  $\Delta PC_{pred}$  was significant both for patients with and without prior cisplatin, in one case the y-intercept was negative and in the other positive (Table II). For the 49 first courses of therapy, the equations appeared to underestimate the change in platelet count less frequently for courses preceded by cisplatin therapy than those not preceded by cisplatin therapy (13% versus 49%,  $p=0.1$ ) (Table III). If data from all 84 courses of carboplatin therapy are examined, the proportion of courses in which the equations underestimate the change in platelets is significantly higher in courses preceded by cisplatin therapy (51% versus 8%,  $p=0.01$ ).

Several factors could contribute to an underprediction of the change in platelet counts. First, other antineoplastics could add to the myelosuppressive effects of carboplatin. The majority of patients were receiving other chemotherapy in addition to carboplatin (see results). Additional chemotherapy received by the patients in our study routinely causes a predominance of leukopenia over thrombocytopenia. The type of combination chemotherapy received by the patients in Egorin et al's study was not reported, making comparison difficult.<sup>14</sup> For the purposes of this study, it was assumed that carboplatin would produce the same degree of thrombocytopenia whether used in combination or alone. During tests of the Egorin et al formulas, Belani and his colleagues treated two groups of patients with 75% of the carboplatin dose calculated from the equation, as a precaution against added myelosuppression from combination chemotherapy.<sup>17</sup> The observed reduction in platelets with combination therapy (etoposide 80mg/m<sup>2</sup> and carboplatin) was essentially equal to

the reduction in platelets which occurred with carboplatin alone.

A second important point to address is the validity of the relationship between CrCl and carboplatin clearance. From CrCl and plasma platinum measurements for 19 courses of therapy, seven of which represented CrCl  $\geq 60$  mL/min, a linear relationship between carboplatin clearance (i.e., ultrafilterable platinum, total body clearance [Cl<sub>TB</sub>]) and CrCl (Cl<sub>TB</sub> = 0.92CrCl + 36.7, r = 0.82) was established.<sup>13</sup> Based on an r-value of 0.82, only 67% of the variability in platinum clearance is accounted for by the measured CrCl. Other unidentified factors also contribute to patient variability in clearance of the drug. In our case, CrCl was estimated from measurement of serum creatinine using the Cockcroft-Gault formula<sup>15</sup>; a formula chosen because it had been shown to be a reasonably accurate estimate of GFR in cancer patients.<sup>18</sup> Using the Cockcroft-Gault formula to estimate CrCl, correlation of  $\Delta PC_{obs}$  and  $\Delta PC_{pred}$  was better for those patients with CrCl < 60 mL/min than those with CrCl  $\geq 60$  mL/min (r = 0.97 versus r = 0.69; Table II), and the equations underestimated the observed change in platelets in fewer patients with low CrCl. This may indicate that CrCl was being overestimated in the upper range of CrCl values, hence underestimating carboplatin's effects on platelets.

An issue which the dosing prediction equations do not address is whether there is a correlation between thrombocytopenia and tumor response. Although there is a correlation between percent change in platelets and AUC of ultrafilterable platinum and there appears to be a relationship between AUC and tumor response,<sup>19</sup> further research is needed to determine the correlation between thrombocytopenia and tumor response.<sup>19-21</sup> It would seem, however, that the maximally tolerated dose of an antineoplastic agent for a patient would result in the best tumor response.<sup>7,8</sup>

In conclusion, the results of this study indicate that the changes in platelet count predicted from the Egorin et al dosing equations for carboplatin correlate reasonably well with the observed reduction in platelet counts. These dosing equations could be used to calculate initial carboplatin dosages for a patient, particularly if that patient has diminished renal function. Estimating renal function by the Cockcroft-Gault formula does not appear to unduly compromise the validity of the dosing equations for patients with CrCl < 60 mL/min. The correlation of predicted and observed change in platelet counts in heavily pretreated patients is poorer than reported in the literature. Despite the poorer correlation, the proportion of patients for which the equations underestimate the reduction in platelets by  $> 25 \times 10^9$ /L is no greater for the heavily pretreated patients than other patients.

Two concerns, which were not addressed in the initial development of the dosing equations, need to be explored in order to facilitate revision of the equations and improve accuracy: the effects of prior cisplatin therapy and of repeated dosing with carboplatin. ☒

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