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Carboplatin pharmacokinetics in young children with brain tumors

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Abstract *Purpose*: The pharmacokinetic parameters and maximal tolerated systemic exposure were determined for carboplatin in young children given in combination with cyclophosphamide and etoposide. *Patients and methods*: Carboplatin was administered as part of a multiagent chemotherapy regimen to 21 pediatric patients less than 5 years of age with newly diagnosed, malignant central nervous system tumors. Patients received cyclophosphamide, 1.2 g/m^2, on day 1 and carboplatin on day 2 followed by etoposide, 100 mg/m^2, each day. Carboplatin doses were calculated to achieve a targeted area under the serum concentration versus time curve (TAUC) of 5, 6.5 or 8 mg/ml . min based on each patient's measured glomerular filtration rate (GFR). Carboplatin pharmacokinetic parameters were determined after course 1 and then after every third course of therapy. *Results*: The median carboplatin clearance and GFR after course 1 were 118 and 98 ml/min per m^2, respectively. Targeted doses based on measured GFR reliably achieved the TAUC for carboplatin. The median (range) carboplatin clearance for four children less than 1 year of age was 76 (66–84) ml/min per m^2, significantly lower ($P = 0.05$) than the value of 131 (80–158) ml/min per m^2 for children from 1 to 4 years of age. The mean carboplatin clearance declined by 23% in 12 patients studied from course 1 to course 4 of therapy. The decrease was greater than 20% (range 20–53%) in 7 of the 12 patients studied. *Conclusion*: Carboplatin clearance for children aged between 1 and 4 years at diagnosis is approximately 45% higher than previously reported for pediatric patients, but declines after four courses of therapy. For children less than 1 year of age, carboplatin clearance per square meter is approximately 40% lower than patients 1 to 4 years of age. There are corresponding differences in GFR that provide a plausible explanation for the age and therapy-related changes in carboplatin clearance. Toxicity was acceptable for patients treated at a TAUC of 6.5 mg/ml . min for carboplatin given with etoposide and cyclophosphamide. The average carboplatin dose required for this AUC was 767 mg/m^2.

Key words Carboplatin · Pharmacokinetics · Glomerular filtration rate · Pediatrics · Brain tumors

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Introduction

Chemotherapy as the initial treatment for central nervous system (CNS) tumors in young children offers the potential for improved response rates and reduced CNS toxicity but consistently effective regimens with acceptable toxicity have not yet been identified [7]. Cisplatin and carboplatin have shown activity as single agents and in combination with other drugs in both recurrent and newly diagnosed pediatric malignancies including CNS tumors [1, 2, 6]. However, cisplatin is

associated with dose-limiting nonhematological toxicities [17] and, when given in combination with other agents, produces serious hematological toxicity leading to treatment delays with increased risk of infectious complications. Carboplatin has similar antitumor activity but shows less ototoxicity, and renal toxicity, and results in less nausea, vomiting and neutropenia than cisplatin [2, 6]. Carboplatin combined with etoposide has shown activity for medulloblastoma and other small round-cell tumors in children [8]. The addition of cyclophosphamide to carboplatin and etoposide was based on the established role of alkylating agents for CNS tumors and to increase the intensity of therapy to improve response rates. Previous experience has shown that a similar regimen could be given with acceptable toxicity [11].

Carboplatin is primarily eliminated by the kidney, and systemic clearance is highly variable even in patients with normal renal function. Relationships between renal function, as assessed by glomerular filtration rate (GFR), and carboplatin clearance have been established in adults and older children and these relationships have proven useful for adjusting doses to minimize differences in systemic exposure commonly observed with fixed-dose regimens adjusted only for body surface area (BSA) [3, 9, 11, 13, 14]. Moreover, the clinical importance of interpatient variability in systemic exposure has been demonstrated by studies defining correlations between the carboplatin area under the concentration verses time curve (AUC) with clinical response and toxicity [9,11].

The possible influence of age or other patient characteristics on carboplatin pharmacokinetics and dose requirements for pediatric patients has not been carefully addressed. Previous studies at St Jude Children's Research Hospital (SJCRH) [11–13] have suggested a trend towards higher carboplatin clearances for children under 5 years of age. Similarly, a recent study [14] of 22 patients found a median carboplatin clearance of 76 ml/min per m^2 in children less than 5 years of age versus 64 ml/min per m^2 in older children. Mean carboplatin clearance is 90 ml/min per m^2 in newly diagnosed pediatric patients [12, 13] but only 47 ml/min per m^2 in heavily pretreated pediatric patients [10]. Collectively, these studies indicate a three- to fourfold range for carboplatin clearance in pediatric patients with no clinically discernible renal dysfunction. The relative contribution of age, prior therapy, extent of disease or other patient characteristics to the variability in carboplatin clearance remains unclear and there is little prior pharmacokinetic data relevant to younger pediatric patients with newly diagnosed brain tumors requiring aggressive chemotherapy.

The primary objectives for this study were to determine the pharmacokinetic parameters and maximal tolerated systemic exposure [5] for carboplatin when used in combination with fixed doses of cyclophosphamide and etoposide in children less than 5 years of age with newly diagnosed brain tumors. Additionally, we prospectively studied the precision and bias of the previously established relationship between carboplatin clearance and measured GFR from older children [11,13] for predicting doses required to achieve a targeted systemic exposure in these younger patients.

Patients and methods

Patient selection and treatment protocol

Children with newly diagnosed, histologically proven primary malignant CNS tumors were enrolled on a multiagent chemotherapy protocol designed to delay the use of radiotherapy. This report details the pharmacokinetic studies carried out as part of the ongoing clinical protocol conducted at SJCRH and Duke University Medical Center. The protocol was approved by the respective institutional review boards and consent was obtained for each patient from a parent or guardian. All patients were less than 5 years of age at diagnosis, and had adequate hepatic (total bilirubin < 1.5 mg/dl, SGPT < 100 u/dl) and renal function (normal serum creatinine for age), and a life expectancy of at least 8 weeks. With the exception of biopsy or resection of tumor, no patient had received prior therapy.

Doses of carboplatin were calculated, as described below, to achieve escalating levels of systemic exposure administered in combination with fixed doses of cyclophosphamide and etoposide. On day 1 of the 2-day treatment cycle, patients received cyclophosphamide, 1.2 g/m^2, given intravenously (IV) with hydration beginning 2 h before and continued for 12 h following the dose. Mesna, 300 mg/m^2, was administered as a 15-min IV infusion immediately before, and at 3 and 6 h following cyclophosphamide. Etoposide, 100 mg/m^2, was administered as a 1-h infusion on day 1 following cyclophosphamide and on day 2 following carboplatin. Carboplatin was administered on day 2 as a 1-h infusion followed by 6 h of hydration. Cycles were repeated every 21 days or as soon as the absolute granulocyte count was greater than or equal to 1000 per mm^3 and the platelet count was greater than or equal to 75 000 per mm^3.

The initial phase of this clinical trial was designed to determine the tolerance to three levels of systemic exposure of carboplatin given with cyclophosphamide and etoposide as outlined above. Doses of carboplatin were adjusted to achieve a targeted area under the concentration versus time curve of 5, 6.5 or 8 (TAUC; units of mg/ml . min) based on carboplatin clearances predicted from the measured GFR for each patient. GFR was determined by technetium 99-diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA) serum clearance [16]. The carboplatin dose was calculated to achieve a specified TAUC from the measured GFR based on a regression equation previously evaluated in a cohort of older pediatric patients [11, 13]:

$$\text{Carboplatin dose (mg/m}^2) = \text{TAUC}[(0.93 \times \text{GFR}) + 15]$$

GFR was measured prior to the first dose of carboplatin and then repeated before every third or fourth course of treatment or earlier if there was more than a $> 20\%$ increase in the baseline creatinine level or other clinical or laboratory evidence to suggest renal dysfunction. A maximum value of 100 ml/min per m^2 for GFR was used for dosage adjustments. Filgrastim (G-CSF) was used in all patients on days 3–16 as a single daily dose of 10 μg/kg administered subcutaneously starting 24 h after chemotherapy.

Pharmacokinetic studies

Carboplatin pharmacokinetic studies and GFR measurements were performed for course 1 and then at courses 4, 7, 10 and 13. Blood

samples (4 ml) were obtained at 1, 3, 8, and 12 h after the end of the carboplatin infusion. Samples were collected in heparinized tubes, placed on ice immediately, and centrifuged for 5 min at 3000 *g*. Plasma was separated and 1 ml of plasma was centrifuged for 15 min at 3000 *g* to obtain ultrafiltrate (Centifree Micropartition tubes, Amicon Division, W.R. Grace and Co., Beverly, Mass.). Plasma ultrafiltrate was stored at $-20^{\circ}C$ until analysis for elemental platinum by flameless atomic absorption spectroscopy as previously described [13].

A one-compartment model was fitted to the measured carboplatin concentrations for each individual using Bayesian estimation. Each observation was weighted by an estimate of the variance for the model prediction. Model parameters were assumed to be independent and normally distributed with mean values and variances based on previous studies at SJCRH [13]. The volume (V) and elimination rate constant (k) were estimated and the clearance (CL) and the elimination half-life ($t_{1/2}$) were calculated. The measured AUC (MAUC) was calculated by dividing the actual dose administered by the carboplatin clearance. Adapt II software was used for pharmacokinetic modeling (Biomedical Simulation Resource, University of Southern California, Los Angeles, Calif.).

The maximal tolerated systemic exposure for this study was defined as the TAUC below the one in which treatment-limiting toxicity was experienced. Treatment-limiting toxicity was defined as grade III/IV nonhematologic toxicity with the exclusion of grade III nausea or vomiting, grade III hepatic toxicity returning to grade I prior to the next treatment, or grade III fever, according to the National Cancer Institute Common Toxicity Criteria. Grade IV hematologic toxicity was defined as neutropenia or thrombocytopenia for 6 days or more. When three patients completed the first cycle of a particular TAUC without experiencing treatment-limiting-toxicity, the TAUC was escalated to the next level. If treatment-limiting toxicity occurred in one of three patients, three additional patients were enrolled at that level of systemic exposure. If no further treatment-limiting toxicity occurred, escalation was continued. If two patients incurred treatment-limiting toxicity, all subsequent patients were enrolled at the preceding level of systemic exposure.

Comparative and descriptive statistics were determined using Statview II software (Abacus Concepts, Berkeley, Calif., 1987). The Wilcoxon signed ranks test, and the Mann-Whitney test were used to test the differences between carboplatin clearances. Linear regression was used to evaluate the correlation between patient characteristics and carboplatin clearance. Bias was evaluated by calculating the median, signed difference between the model predicted and measured clearance and the targeted and measured AUC. Precision was evaluated by dividing the absolute difference between the measured and predicted clearance or TAUC by the predicted value expressed as a percent of the expected value. This allowed assessment of precision for different TAUC and predicted clearance values.

Results

Carboplatin pharmacokinetic studies and GFR measurements were obtained during 51 courses of therapy in 21 of the initial 35 patients enrolled on this therapeutic protocol. The remaining 14 patients were not included because informed consent for the pharmacokinetic studies could not be obtained. Pharmacokinetic data were available for all 21 patients during course 1, 12 patients during course 4, 9 patients during course 7, 5 patients during course 10 and 4 patients during course 13. The median age of the patients with pharmacokinetic data at diagnosis was 1.7 years (range 0.2 to 4.2) and median BSA was 0.53 m^2 (range 0.30 to 0.75). Median values for blood urea nitrogen and serum creatinine prior to course 1 were 6.0 mg/dl (range < 2.0 to 14) and 0.3 mg/dl (range 0.2 to 0.4). Six patients received doses to achieve a TAUC of 5 mg/ml . min, with pharmacokinetic data available for four, and 24 patients received doses to achieve a TAUC of 6.5 mg/ml . min and pharmacokinetic data were obtained in 15. Dose-limiting toxicity was not observed in the patients treated at an AUC of 5 or 6.5 mg/ml . min. Five patients were treated at a TAUC of 8 mg/ml . min, and pharmacokinetic data were available for two. Two of five patients developed unacceptable hematopoietic toxicity (grade IV neutropenia or thrombocytopenia for 6 days or more). One patient incurred grade IV hematopoietic toxicity after course 2 which required a 20% reduction in cyclophosphamide for subsequent courses. Grade IV hematopoietic toxicity persisted and the TAUC for carboplatin was decreased to 6.5 mg/ml . min. The second patient suffered moderate hematopoietic toxicity after the first three courses and was taken off protocol after course 4 due to persistent hematopoietic toxicity despite a 20% decrease in the cyclophosphamide dose following course 3. All subsequent patients were treated at a TAUC of 6.5 mg/ml . min as the maximal tolerated systemic exposure.

Carboplatin pharmacokinetic parameters obtained after course 1 are summarized in Table 1. Carboplatin clearance (ml/min) after course 1 correlated with measured GFR ($r^2 = 0.65$), BSA ($r^2 = 0.65$), body weight ($r^2 = 0.58$) and age ($r^2 = 0.44$). The relationship between GFR and carboplatin clearance is shown in Fig. 1. The correlation between carboplatin clearance and GFR when normalized to BSA was lower ($r^2 = 0.39$). For course 1, the median (range) carboplatin clearance for children less than 1 year of age ($n = 4$) was 76 (66–84) and was significantly lower ($P < 0.05$) than for children over 1 year of age, 131 (80–158) ml/min per m^2 ($n = 17$). To further examine the relationship of age and carboplatin clearance, 11 patients with newly diagnosed large-cell lymphoma from a previous study [13] between the ages of 5 and 17 years who received carboplatin at similar doses were compared with the patients reported here after course 1 (Fig. 2). The median carboplatin clearance for

Table 1 Carboplatin pharmacokinetic parameters. The values are for course 1 of therapy for all 21 patients

	Median (range)	CV (%)
Elimination rate (h^{-1})	0.58 (0.42–0.76)	19
Elimination half-life (h)	1.19 (0.92–1.64)	19
Volume (l)	6.66 (2.11–11.26)	41
(l/m^2)	11.77 (7.10–17.94)	27
Clearance (ml/min)	66 (24–112)	40
(mL/min per m^2)	118 (66–158)	27

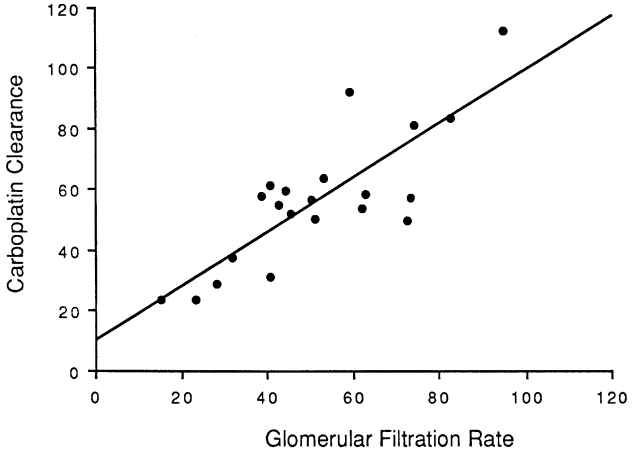

Fig. 1 Carboplatin clearances (ml/min) and GFR (ml/min) in 21 patients after course 1 were highly correlated ($y = 0.97x + 11.65$, $r^2 = 0.65$)

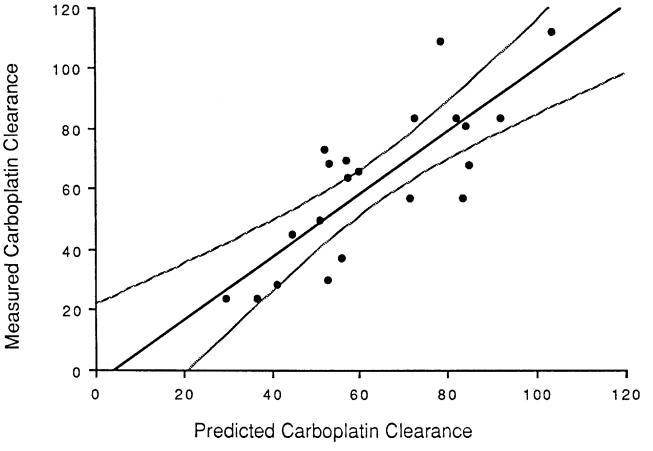

Fig. 3 Predicted and measured carboplatin clearance (ml/min) in 21 patients after course 1 were highly correlated ($y = 1.04x - 3.97$, $r^2 = 0.65$). Shown are the regression line and 95% confidence interval for predicted values

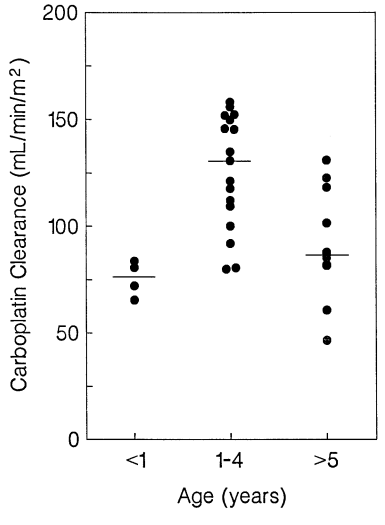

Fig. 2 Median values (*bars*) and individual carboplatin clearances (*closed circles*) are shown for 32 patients from 0.2 to 17 years of age determined for course 1 of chemotherapy. Data from patients more than 5 years of age are from reference 13

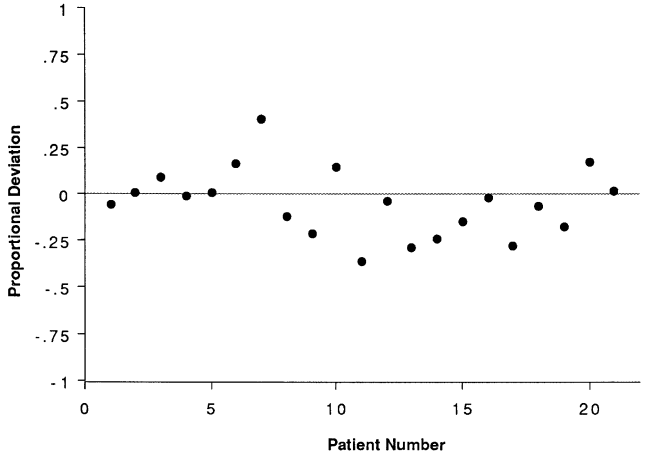

Fig. 4 The precision of achieving the target AUC is shown by determining the proportional deviation (MAUC − TAUC/TAUC) for each of the 21 patients studied

children between 1 and 4 years of age (131 ml/min per m^2) was significantly higher ($P < 0.05$) than for children between 5 and 17 years of age (87 ml/min per m^2). Despite the significant differences for median carboplatin clearance between patients of different age groups, the intersubject variability within age ranges yielded substantial overlap and only a poorly predictive relationship between age and carboplatin clearance. However, the variability in carboplatin clearance between subjects is substantially accounted for by the measured GFR.

Carboplatin clearance could be predicted from GFR with minimal bias and good precision. As shown in Fig. 3, the predicted and measured carboplatin clearances were highly correlated ($r^2 = 0.65$). The median values for predicted (57 ml/min) and measured (66 ml/min) carboplatin clearance in 21 patients after course 1 were not significantly different ($P = 0.65$). Of 21 patients, 15 (71%) were within 20% of the TAUC (Fig. 4). There were seven patients at course 1 with a measured GFR greater than 100 ml/min per m^2 who thus received a dose based on the maximum value of 100 rather than the actual GFR. The median GFR for these seven patients was 127 ml/min per m^2 with a range of 106 to 161 ml/min per m^2. The median measured carboplatin clearance of 146 ml/min per m^2 was not significantly different from the predicted value suggesting that even at high GFR values, dose adjustments should be based on the measured GFR. Three of five patients with a MAUC that was more than 20% below the targeted values received carboplatin doses less than predicted from the dose

Table 2 GFR, carboplatin clearance and dose. The values are medians (range) for each treatment cycle. The doses are the actual amounts given for TAUCs that ranged from 5 to 8 mg/ml . min

	Course number				
	1	4	7	10	13
Number of patients	21	12	9	5	4
GFR (ml/min per m^2)	98 (52–161)	95 (45–150)	73 (56–114)	87 (61–144)	93 (56–119)
Clearance (ml/min per m^2)	118 (66–158)	82 (57–161)	95 (76–160)	80 (66–122)	95 (71–98)
Dose (mg/m^2)	684 (359–864)	543 (340–702)	466 (400–629)	475 (373–587)	467 (379–498)

calculation equation due to the use of a maximum GFR of 100 ml/min per m^2 for dose calculation. Both predicted clearance and TAUC were found to have no appreciable bias (1.52 ml/min and -0.33 mg/ml . min, respectively) and acceptable precision (22% and 13%, respectively).

The median values for carboplatin clearance, GFR and dose are shown in Table 2 for each course of therapy. There was no discernible difference in either GFR or carboplatin clearance between courses for the median values for all courses but follow-up data were not available for all patients. However, when only patients with carboplatin clearances available for both course 1 and 4 were compared ($n = 12$), there was a significant decrease ($P = 0.05$). Median carboplatin clearance was 120 ml/min per m^2 and 82 ml/min per m^2 for course 1 and course 4, respectively. Carboplatin clearance decreased more than 20% in 7 of 12 patients with a range of 20% to 53%. The clearance was 20% higher in one patient and the remaining four patients showed no appreciable difference from course 1 to course 4.

Discussion

The maximal tolerated systemic exposure, defined by the AUC, for carboplatin when given with moderate doses of cyclophosphamide and etoposide was 6.5 mg/ml . min. The average dose required to achieve an AUC of 6.5 mg/ml . min for these patients was 767 mg/m^2 for course 1 of therapy based on the median measured carboplatin clearance of 118 ml/min per m^2. This high dose of carboplatin was well tolerated through the first two cycles of treatment despite being administered in combination with cyclophosphamide and etoposide. In contrast, a previous report [4] of single-agent carboplatin at a dose of 560 mg/m^2, without consideration of renal function, caused severe thrombocytopenia and a decrease of greater than 20% in GFR in 5 of 11 children evaluated. However, these patients had received prior therapy including cisplatin which may have reduced carboplatin clearance or predisposed the patients to toxicity. The patients in this study differed in that they were newly diagnosed and younger.

The median clearance for carboplatin of 118 ml/min per m^2 for course 1 was approximately 50% higher than previously reported values [14, 15]. The higher clearance in these newly diagnosed patients persisted even when patients of similar age were compared. This striking difference may be explained by the fact that 20 of the 22 patients studied by Newell et al. [14] had received prior chemotherapy, and previous studies have suggested that patients with recurrent disease or prior therapy may have lower carboplatin clearances [10, 11, 15]. The possible influence of cumulative therapy on carboplatin clearance is supported by the subset of patients with data available for multiple courses who showed a significant decrease. Unfortunately, we were not able to obtain follow-up data in all patients which precludes drawing definitive conclusions regarding changes in carboplatin clearance over multiple courses of therapy. The magnitude of change in carboplatin clearance and dose requirements within and between patients highlight the potential benefit for individualized doses.

The clinical rationale for patient-specific dosage regimens for carboplatin is motivated by the presumption of a narrow therapeutic range and substantial intersubject pharmacokinetic variability. The increased hematopoietic toxicity noted in this study, with only a modest increase in AUC from 6.5 to 8 mg/ml . min, is consistent with prior studies in adults and children demonstrating a narrow therapeutic range for carboplatin. [9, 11, 12]. The extent of pharmacokinetic variability is more difficult to assess. The relatively modest coefficient of variation for carboplatin clearances from course 1 might suggest that fixed doses, adjusted for body size, would not result in large differences in systemic exposure. However, the significant changes in carboplatin clearance over multiple courses of therapy and the apparent age-related differences in renal function and drug clearance can result in sufficient intersubject variability in systemic exposure to impact on the risk of toxicity or inadequate therapy.

The use of measured GFR was quite accurate in predicting carboplatin clearance (Fig. 1) and in achieving a targeted systemic exposure (Fig. 4). In the context of defining the toxicity profile for increasing levels of systemic exposure, the use of patient-specific doses substantially improves the efficiency of a phase I/II study by minimizing the confounding variable of intersubject differences in systemic drug clearance [5]. Given the availability of a reliable measure of GFR, such as the serum clearance of a radiopharmaceutical substrate

(e.g. ^{99m}Tc-DTPA), targeted doses of carboplatin can improve the precision of therapy. It remains to be demonstrated whether the increased cost and inconvenience are necessary for all patients receiving carboplatin. The differences observed for carboplatin clearance in pediatric patients of different ages and with multiple courses of therapy provide strong incentive to target doses of carboplatin based on reliable measures of GFR.

In summary, when carboplatin was given with etoposide and cyclophosphamide, the maximal tolerated systemic exposure for pediatric patients less than 5 years of age with newly diagnosed brain tumors was not appreciably different from that reported previously for single-agent carboplatin in adults [9] or children [4]. However, the dose required to achieve a TAUC of 6.5 mg/ml . min at diagnosis was substantially higher in these patients less than 5 years of age. It seems quite likely that the single agent maximal tolerated systemic exposure for carboplatin would be even greater, as the hematopoietic toxicity is potentially additive with etoposide and cyclophosphamide. The higher carboplatin dose in younger patients is explained by their higher GFR. Although pharmacokinetic variability for carboplatin is modest at the outset of therapy, the narrow therapeutic range, the potentially reduced clearance and dose requirements over multiple courses of therapy and the difficulty of reliably predicting age-dependent pharmacokinetic differences provide substantial clinical motivation for targeted carboplatin dosing.

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