Published in final edited form as:

Pediatr Blood Cancer. 2010 July 15; 55(1): 47–54. doi:10.1002/pbc.22467.

Comparison of Two Methods for Carboplatin Dosing in Children with Retinoblastoma

Steven Allen, BS⁽¹⁾, Matthew W. Wilson, MD^{(2),(4)}, Amy Watkins, MS⁽³⁾, Catherine Billups, MS⁽³⁾, Ibrahim Qaddoumi, MD^{(1),(5)}, Barrett H. Haik, MD^{(2),(4)}, and Carlos Rodriguez-Galindo, MD^{(1),(5)}

⁽¹⁾ Department of Oncology, St. Jude Children's Research Hospital Memphis, TN

⁽²⁾ Department of Surgery, St. Jude Children's Research Hospital Memphis, TN

⁽³⁾ Department of Biostatistics, St. Jude Children's Research Hospital Memphis, TN

⁽⁴⁾ Department of Ophthalmology (Hamilton Eye Institute), University of Tennessee Health Sciences Center Memphis, TN

⁽⁵⁾ Department of Pediatrics, University of Tennessee Health Sciences Center Memphis, TN

Abstract

Background—Carboplatin is the most effective drug in retinoblastoma but systemic clearance is variable in young patients. While most regimens use a flat dose, individualized targeting may provide a more adjusted systemic exposure.

Patients and Methods—We compared carboplatin doses between two groups of children with retinoblastoma that were treated using a flat dose of 560 mg/m² or a targeted AUC of 6.5 using a modified Calvert formula.

Results—Ninety-eight patients with retinoblastoma received a total of 576 cycles of carboplatin (median 8 cycles). Fifty patients (51%) received a fixed dose per m², 32 (33%) received a dose based on AUC, one patient received fixed dose per kilogram, and in 15 patients a combination AUC and fixed doses was used. The median cumulative carboplatin dose (mg/m²) for patients who received 8 cycles using fixed per m² dosing was 2151.8 (range, 1414.2 – 2852.0), compared to 1104.1 for 9 patients who received 8 cycles using Calvert dosing (range, 779.0 – 1992.7) ($p < 0.001$). For cycles given using AUC, the median percentage of the hypothetical fixed per m² dose was 70% (range, 48%–134%). Younger patients had larger differences. Patients receiving carboplatin based on fixed per m² dosing were 3.0 times more likely to have a platelet transfusion (95% confidence interval, 1.3–7.3).

Conclusions—Carboplatin administration needs to consider the changes in renal function occurring during the first months of life. The use of a targeted AUC provides the most accurate method; however, mg per kg of body weight dosing is a very reliable alternative method.

Keywords

Carboplatin; Retinoblastoma; Glomerular filtration rate

Correspondence: Carlos Rodriguez-Galindo, MD, Dana-Farber Cancer Institute and Children's Hospital, Harvard Medical School, 44 Binney Street, Boston, MA 02115, Phone: 617-632-4580, Fax: 617-632-5710, carlos_rodriguez-galindo@dfci.harvard.edu.

The authors have no conflicts of interest to disclose.

Introduction

Retinoblastoma is the most frequent neoplasm of the eye in childhood representing 2.5% to 4% of all pediatric cancers, and 11% of cancers in the first year of life.¹ Treatment of retinoblastoma is individualized; factors to be considered include laterality, vision potential, and intraocular and extraocular staging. Most patients with unilateral disease undergo upfront enucleation, and adjuvant chemotherapy, usually with carboplatin-containing regimens, is given only in those cases where high risk histological factors are identified.² Patients with bilateral disease represent a more challenging group; a more conservative approach is taken, and treatment incorporates up-front chemotherapy followed by aggressive focal therapies.² Different chemotherapy combinations are used, although the best results are achieved with a combination of vincristine, carboplatin and etoposide.^{3–6,7} For patients with early intraocular stages, a less intensive regimen with vincristine and carboplatin alone is effective.^{5–7}

Carboplatin is considered the single most effective drug for the treatment of this neoplasm and a key agent in all retinoblastoma regimens. Carboplatin is a second generation platinum-containing compound with less nephrotoxicity, neurotoxicity and gastrointestinal toxicity than cisplatin.⁸ Carboplatin is eliminated almost entirely by glomerular filtration, but systemic clearance is highly variable even in patients with normal renal function.⁹ A relationship has been demonstrated between the rate of drug elimination and systemic drug exposure, as defined by the area under the plasma concentration time curve (AUC).^{10–13} Thus, using glomerular filtration rate (GFR) to achieve a target AUC ensures appropriate dosing for patients with lower than or higher than average GFR, who might otherwise receive inadequate treatment. Thrombocytopenia is the major dose-limiting toxicity and highly correlates with AUC.^{9,14} Likewise, the response rate in patients with ovarian cancer has been correlated to the AUC to which patients are exposed.¹⁴

General consensus on carboplatin dosing has not been reached for many pediatric malignancies, including retinoblastoma. While individualized targeting of carboplatin exposure would be ideal in children with cancer, in practicality most regimens use a flat, fixed dose, either per body surface area (500 to 560 mg/m²) or, particularly for young children, per kilogram of body weight (16.6 to 18.6 mg/kg). However, those dosing methods do not take into consideration the changes in renal function occurring during the first years of life, particularly during infancy.¹⁵ Thus, children with retinoblastoma could be particularly vulnerable to over or under carboplatin exposures.

At St. Jude Children's Research Hospital, the initial retinoblastoma regimens used the standard, flat dose of 560 mg/m² for patients with normal renal function, and we recently adopted a targeted approach calculating the AUC using a modified Calvert formula. These two sequential groups of patients offered the unique opportunity to evaluate the differences in carboplatin dosing, exposure, and cumulative amount received, and to evaluate the impact of the different dosing methods on toxicity.

Patients and Methods

Patient Characteristics

Patients diagnosed with retinoblastoma between February 1996 and January 2008, and who received intravenous carboplatin, either as part of a chemoreduction regimen for intraocular disease or after enucleation for high risk histological features, were eligible for this IRB-approved retrospective study. Ninety-eight patients were identified. Table I shows patient characteristics. Fifty-six percent of the patients (n=55) were male. The median age at diagnosis was 8.6 months (range 9 days to 13.6 years). Approximately 70% of the patients

were < 1 year old at diagnosis (n=66) and most (n=90; 92%) were < 2 years of age. Approximately three-fourths of the patients had bilateral retinoblastoma (n=72).

Treatment

Since 1996, St. Jude has treated children with intraocular retinoblastoma in accordance with 3 different chemotherapeutic approaches: the institutional studies RET3 and RET5, and off protocol St. Jude best clinical management (SJBCM) regimens. The RET3 protocol was used between 1996 and 2001, and was composed of 8 cycles of vincristine (V) and carboplatin (C) in 3-week intervals. Carboplatin dosing was 560 mg/m² for patients with GFR 50 ml/min/m², but was adjusted to AUC of 6.5 for patients with lower GFR. For calculating AUC, a modified Calvert formula was used; the carboplatin dose was calculated to achieve a specified AUC from measured GFR based on a regression equation previously evaluated in a cohort of older pediatric patients [$Dose (mg/m^2) = AUC \times [(0.93 \times GFR (ml \text{ min}^{-1} m^2)) + 15]$].^{16,17} The GFR was determined by technetium 99-diethylenetriaminepentaacetic acid (99mTc-DTPA) serum clearance.¹⁸ The SJBCM regimens were used in the transitional period between 2001 and 2005, and patients were treated similarly to RET3, with patients with advanced disease receiving the addition of etoposide (VCE) for 6 cycles. From 2005 to the present, patients have been treated on the RET5 protocol, which consists of VC $\times$ 8 cycles for patients with early intraocular disease, and VC $\times$ 6 cycles and vincristine and topotecan (VT) $\times$ 5 cycles for patients with advanced disease. In RET5, all patients receive carboplatin based on AUC of 6.5. Patients with enucleated retinoblastoma with high-risk histological features treated on RET5 were also included in this analysis. Those patients were treated with adjuvant chemotherapy consisting of a combination of 3 cycles each of VCE and vincristine, cyclophosphamide and doxorubicin (VCD) or 6 cycles of VCE, depending on the extent of the extraretinal disease.

Seventy-four percent of patients (n=73) received 8 cycles of chemotherapy. The distributions of treatment regimens were as follows: RET3 (n=25; 26%), SJBCM (n=50; 51%) and RET5 (n=23; 23%). Fifty patients (51%) received fixed doses of carboplatin per m² (n=50; 51%), while 32 (33%) had dosing based on the modified Calvert formula. There was no difference in gender (p=0.26), race (p=0.65) or laterality (p=1) distributions between patients receiving fixed per m² vs. dosing based on AUC. Patients receiving dosing based on the modified Calvert formula were more likely to be less than 1 year old at diagnosis (75% vs. 52%) (p=0.063). One patient received a fixed dose per kg while 15 patients received carboplatin using a combination of fixed and Calvert dosing as indicated per RET3 protocol (see above).

By treatment regimen, 18 of 25 RET3 patients (72%) received fixed per m² carboplatin dosing, 1 received carboplatin per the Calvert formula, and 6 patients received carboplatin with a combination of Calvert and fixed per m² dosing. All of the RET5 patients received carboplatin using the modified Calvert formula (one of these had a combination of Calvert and fixed per kg). Of the 50 patients treated on SJBCM, 32 (64%) received fixed per m² doses, 9 received carboplatin using the Calvert formula, 1 per kg doses, and 8 patients had a combination of dosing using Calvert and fixed per m² methods.

Statistical Methods

Fisher's exact test was used to compare gender, race (white vs. others), laterality and age at diagnosis (<1 year vs. $\geq$ 1 year) between carboplatin dosing methods. The exact Wilcoxon rank sum test was used to compare cumulative doses of carboplatin between dosing groups stratified by number of cycles. The exact Wilcoxon rank sum test was also used to compare the median carboplatin dose and amount received between patients receiving fixed per m² dosing and modified Calvert dosing. The Spearman correlation coefficient was used to

examine the association between age at diagnosis and hypothetical dose differences during cycle 1 of carboplatin. Generalized linear models were used to investigate the impact of age at diagnosis as a predictor of differences in hypothetical doses. We investigated the association of carboplatin dosing method (Calvert *vs.* fixed per m^2) on toxicity using generalized linear models to account for repeated measures taken on subjects. Toxicity measures were binary response variables.

Results

Median doses and cumulative carboplatin received (Calvert dosing *vs.* fixed per m^2 dosing)

As shown in Table II, patients who received only fixed per m^2 dosing received higher cumulative doses of carboplatin. The median cumulative carboplatin dose (mg/m^2) for 27 patients who received 8 cycles using fixed per m^2 dosing and had complete dose data was 2151.8 (range, 1414.2 – 2852.0), compared to 1104.1 for 9 patients who received 8 cycles using Calvert dosing and had complete dose data (range, 779.0 – 1992.7). This difference was statistically significant ($p < 0.001$). Similar differences were seen among the group of patients who received 6 cycles and had complete dose data ($p = 0.001$) (Table II).

The median dose (mg/m^2) was lower for patients who received Calvert dosing (457 (range, 296 – 642) *vs.* 560). For patients with Calvert dosing, we calculated the proportion of the carboplatin dose relative to 560 mg/m^2 , the fixed per m^2 dose. Eighty-four percent of those patients (26/31) received less than 560 mg/m^2 . The median proportion was 81.6% (range, 52.9% – 114.6%).

For patients who received fixed per m^2 carboplatin, the median total amount received per patient per cycle was 274.3 (range, 177.0 – 929.0) compared to 196.5 for patients who received carboplatin per the modified Calvert formula (range, 89.0 – 384.0) ($p < 0.001$). The analysis for the above questions used only patients who received all their doses of carboplatin in the same manner (all fixed or all Calvert dosing).

Hypothetical intra-patient dose variations among the dosing methods

We determined the hypothetical differences in carboplatin doses given during each cycle for each patient. For example, if a patient received carboplatin using a fixed per m^2 dosing regimen, we determined what dose would have been administered using the Calvert formula or given as a fixed per kg dose, and vice versa.

Summary statistics for the differences and proportions between administered and hypothetical doses are shown in Table III. These are shown separately for each dosing method. Large median differences in dose and amount were observed between the Calvert and fixed per m^2 dosing. Among 259 cycles that were dosed using the Calvert method and had dose data, the median difference between the Calvert dose and the hypothetical fixed per m^2 dose was $-169 mg/m^2$. The hypothetical fixed per m^2 dose was higher in 90% of the cycles (233 of 259) compared with the administered Calvert dose. We divided the administered Calvert dose by the hypothetical fixed per m^2 dose. For cycles given using Calvert dosing, the median percentage of the hypothetical fixed per m^2 dose was 70% (range, 48% – 134%). For 247 cycles that used the Calvert formula and had data, the median difference between the amount administered per cycle using the Calvert formula amount and the hypothetical fixed per kg was only 13 mg. The median proportion (Calvert/hypothetical fixed per kg amount) was close to 100% (109.4%).

For cycles administered with fixed per m^2 dosing, the median difference in the fixed dose compared to the hypothetical Calvert dose was 45 mg/m^2 . Sixty-four percent (256/398) of

cycles had higher fixed per m^2 doses than hypothetical Calvert formula doses. The fixed per m^2 amounts were also more than hypothetical amounts using fixed per kg dosing (median, 78.6). The median proportion of the fixed per m^2 dose relative to the hypothetical Calvert dose was slightly higher than 100% (108.8%).

Association of carboplatin dosing differences with age

Since renal function matures gradually during the first year of life, we wanted to investigate whether younger children were more susceptible of being exposed to higher doses of carboplatin when a fixed dosing method was used. We first investigated this by looking at data for the first cycle of carboplatin only. Of the 55 patients who received carboplatin fixed per m^2 for the first cycle, 54 had complete dose data; 65% of these patients ($n=35$) received a fixed per m^2 dose of carboplatin that was more than the calculated hypothetical Calvert dose. Figure 1a shows a scatter plot of these proportions (fixed per m^2 dose received/hypothetical Calvert dose) with age at diagnosis. There was evidence that younger patients received higher fixed per m^2 doses of carboplatin compared to hypothetical Calvert doses. The Spearman correlation coefficient was -0.515 (95% bootstrap confidence interval, -0.717 to -0.287) ($p<0.001$). Similarly, there was evidence that younger patients received lower Calvert doses of carboplatin compared to hypothetical fixed per m^2 doses. Figure 1b shows a scatter plot of these proportions (Calvert dose received/hypothetical fixed per m^2 dose) with age at diagnosis. The Spearman correlation coefficient was 0.823 (95% bootstrap confidence interval, 0.643 to 0.914) ($p<0.001$).

We also looked at changes in renal function over time, and we observed that GFR values were increasing slightly over time. Older age at diagnosis was associated with higher GFR ($p<0.001$) (Figure 2). Despite these changes, for patients dosed via the Calvert method, doses were stable over time.

Association of carboplatin dosing with toxicity

We investigated the association of carboplatin dosing methods on toxicity using generalized linear models. All toxicity measures were binary response variables. Table IV shows the number of cycles with toxicity by dosing method. Eight percent and 12% of cycles given as Calvert method and fixed per m^2 , respectively, resulted in admission for fever and neutropenia. Proportions of cycles with red blood cell transfusions were similar (approximately 11% for both methods). The proportion of cycles requiring platelet transfusions was higher when fixed per m^2 dosing was used (10% vs. 4%). In statistical analyses that accounted for repeated measures taken on subjects, there was no evidence that admission for febrile neutropenia, requirement for red blood cell transfusion or delay in chemotherapy administration was significantly different based on the formula used (Calvert vs. fixed per m^2) (Table V). However, the need for platelet transfusions was significantly different by dosing method. Patients receiving carboplatin based on fixed per m^2 dosing method were 3.0 times more likely to have a platelet transfusion compared to patients dosed with the Calvert formula (95% confidence interval, $1.3 - 7.3$).

For fixed per m^2 cycles, we investigated the difference between the fixed per m^2 dose and the hypothetical Calvert dose as a predictor of toxicity. The difference in fixed per m^2 doses and hypothetical Calvert doses was a significant predictor of platelet transfusions ($p=0.003$). The odds ratio showed that patients with a 10-unit increase in the difference were 1.1 times more likely to have a platelet transfusion (95% CI, $1.03 - 1.13$). There was no evidence that differences were significantly associated with the other toxicity measures (admission for febrile neutropenia, need for red blood cell transfusion, or treatment delay).

We also investigated the possible confounding effect of etoposide on toxicity. Of the 50 patients who received carboplatin as fixed per m^2 , 6 (12%) received etoposide. Of the 32 patients dosed with the Calvert formula, 7 (22%) received etoposide. The proportions of patients receiving etoposide was not significantly different between the two dosing methods ($p=0.35$). In models adjusted by whether or not patients received etoposide, there remained no evidence that admission for febrile neutropenia, requirement for red blood cell transfusion, or delay in chemotherapy administration was significantly different by dosing method (Calvert vs. fixed per m^2). Adjusted by whether or not patients received etoposide, the need for platelet transfusions remained significantly different by dosing method. Given the retrospective nature of the study and the lack of consistent renal and hearing function data, the impact of the dosing method on renal and auditory functions could not be assessed.

Discussion

As treatments for childhood cancer evolve and cure rates increase, minimization of toxicity and development of treatments that account for the physiological changes occurring in the context of the developing child must be considered. This is particularly relevant in the treatment of children with retinoblastoma; patients are diagnosed very early in life, during a period of rapidly evolving organ function. This context dictates the approach to their disease; visual function preservation and delaying or avoiding radiation therapy are major treatment objectives. Similarly, the choice of carboplatin over the more toxic cisplatin responds to the need to minimize toxicity. However, carboplatin is eliminated almost entirely by glomerular filtration and systemic exposure may vary greatly as renal function matures during the first years of life.

With the purpose of evaluating the best method of carboplatin dosing, we compared carboplatin exposures between patients treated with a fixed mg/m^2 dose and patients receiving individualized AUC dosing. Based on earlier carboplatin pharmacokinetic studies^{19,20} the initial retinoblastoma regimens used a standard dose of $560 mg/m^2$, and only patients with low GFR received a dose adjusted to their renal function. In the most recent era, we changed our approach to individualize carboplatin dosing based on AUC to all patients, regardless of renal function. A comparison of carboplatin doses and cumulative exposure between both approaches revealed that flat dosing results in higher doses and cumulative exposure than using the modified Calvert formula. In a similar study, Jodrell et al.¹⁴ performed a retrospective analysis of 1028 patients included in phase II studies for ovarian cancer; patients had been treated on a flat mg/m^2 basis, but had creatinine clearance measures allowing to perform a retrospective estimate of the AUC to which they had been exposed. The study showed a progressive increase in hematological toxicity with increasing AUC while the response rate appeared to plateau.

Carboplatin is particularly susceptible to physiological modeling to predict individualized doses. The first model developed by Egorin et al. used measures of renal function and body size to target a dose to a desired level of the pharmacodynamic endpoint, thrombocytopenia.²¹ The second method, developed by Calvert et al. simply calculated a dose designed to achieve a pre-defined AUC on the basis that AUC would be a more meaningful indicator of clinical effect.¹¹ Chatelut et al. used a population pharmacokinetics approach to derive a formula based directly on weight, age, and serum creatinine (not GFR).²² Studies comparing the performance of the Chatelut formula with carboplatin pharmacokinetics have shown that this formula is quite reliable.²³ However, the Calvert method has been more widely adopted largely because it can be applied to combination therapy and to high-dose therapy, situations where the use of thrombocytopenia as an endpoint and the serum creatinine as a measure of renal function would be inappropriate.

The Calvert formula is thus a widely applied algorithm for carboplatin dosing based on patients' GFR as accurately measured using the [^{51}Cr]-EDTA or $^{99\text{m}}\text{Tc}$ -DTPA clearance methods.²⁴ Alternative, more convenient methods of estimating GFR in adults and children have been in use for many years, usually based on a measure of serum creatinine, age, size, and sex of the patient such as in the Cockcroft-Gault²⁵, Jelliffe²⁶, Wright²⁷ and Schwartz²⁸ formulas. However, creatinine is not an ideal filtration marker because it is both filtered by glomeruli and secreted by renal tubules.²⁹ Accordingly, creatinine clearance theoretically exceeds GFR by > 12% in subjects with normal renal function¹³ and when carboplatin doses are calculated using the serum creatinine-based formulas as the estimate of GFR, the AUCs obtained may be significantly lower than those intended.^{13,23} Studies evaluating the accuracy of these alternate methods suggest that they can result in a significant dosing bias.^{30,31,32,33} Thus, modifications of the Calvert formula by estimating GFR from serum creatinine may not be indicated.

There is no clear consensus on the best method for carboplatin dosing in children and yet as in adults, there is a narrow therapeutic range.^{16,19} Most regimens use the maximum tolerated dose of 560 mg/m²,³⁴ which is often adjusted to a per kilogram of body weight dose (18.6 mg/kg) for younger children; individualized dosing targeting a AUC is seldom used for standard regimens, and it is reserved for regimens targeting high exposures, such as the ICE (ifosfamide, carboplatin and etoposide) combination or high-dose chemotherapy regimens with autologous stem cell rescue. However, studies indicate a three to fourfold range for carboplatin clearance in pediatric patients with no clinically discernible renal dysfunction.

The retinoblastoma population is unique in that patients are diagnosed at a very early age, and there is very little data on carboplatin pharmacokinetics in very young children. In our study, the differences in carboplatin dosing were more significant in patients younger than 6 months of age. This is consistent with the available data suggesting that there is a trend towards higher carboplatin clearances for younger children.^{19,35} Tonda et al.²⁰ investigated carboplatin pharmacokinetics in young children with brain tumors; carboplatin clearance (ml/min) correlated with measured GFR, body surface area, body weight and age, and the median carboplatin clearance for children < 1 year was significantly lower than for older children (76 vs. 131 ml/min/m²). Despite the significant differences for median carboplatin clearance between patients of different age groups, the intersubject variability within age ranges results in substantial overlap and a poorly predictive relationship between age and carboplatin clearance.^{17,20} Furthermore, repeated administration of carboplatin may result in reduced GFR and decreased carboplatin clearance during treatment.^{36,19, 20, 37}

In this context, the variability in carboplatin clearance between children is substantially accounted for by the measured GFR, thus the importance of individualized dosing. In a randomized trial in children with cancer, Thomas et al. showed a significant reduction in the variability of the systemic exposure for those patients dosed according to AUC.³⁸ In order to account for the variations in the non-renal clearance related to body size, several versions of the original Calvert formulation exist in the pediatric literature^{16,35,39-42}. However, variations in renal function measurement between clinical centers, as well as misinterpretation of formulas can result in major dosing errors.^{43,44} As shown in our study, calculating carboplatin dose using the mg/kg formula appears to be a reliable method, with minimal differences compared with the modified Calvert formula.

The differences in carboplatin exposure did not correlate with myelosuppression as measured by delays in chemotherapy, admissions for febrile neutropenia or transfusion of red blood cells. However, patients treated with a flat dose had more severe thrombocytopenia requiring a higher number of platelet transfusions. This is consistent with

adult studies showing a clear correlation between carboplatin exposure and thrombocytopenia.^{9,14}

Carboplatin administration needs to consider the changes in renal function occurring during the first months of life, and dosing should be adjusted accordingly. The use of a targeted AUC provides the most accurate method; however, mg per kg of body weight dosing may be a very reliable alternate method.

Acknowledgments

Supported by Grants P30-CA23099 and CA21765, American Lebanese Associated Charities (ALSAC), Research to Prevent Blindness, New York, and St Giles Foundation, New York.

References

1. Young, JL.; Smith, MA.; Roffers, SD.; Liff, JM.; Bunin, GR. Retinoblastoma. In: Ries, LAG.; Smith, MA.; Gurney, JG.; Linet, M.; Tamra, T.; Young, JL.; Bunin, GR., editors. Cancer Incidence and Survival among Children and Adolescents: United States SEER Program 1975–1995. National Cancer Institute; Bethesda, MD: 1999. SEER Program. NIH Pub. No. 99–4649
2. Rodriguez-Galindo C, Chantada GL, Haik B, Wilson MW. Retinoblastoma: Current treatment and future perspectives. *Curr Treat Options Neurol*. 2007; 9:294–307. [PubMed: 17580009]
3. Shields CL, Honavar SG, Meadows AT, et al. Chemoreduction plus focal therapy for retinoblastoma: Factors predictive of need for treatment with external beam radiotherapy or enucleation. *Am J Ophthalmol*. 2002; 133:657–664. [PubMed: 11992863]
4. Nenadov Beck M, Balmer A, Dessing C, Pica A, Munier F. First-line chemotherapy with local treatment can prevent external-beam irradiation and enucleation in low-stage intraocular retinoblastoma. *J Clin Oncol*. 2000; 18:2881–2887. [PubMed: 10920136]
5. Wilson MW, Haik BG, Liu T, Merchant TE, Rodriguez-Galindo C. Effect on ocular survival of adding early intensive focal treatments to a two-drug chemotherapy regimen in patients with retinoblastoma. *Am J Ophthalmol*. 2005; 140:397–406. [PubMed: 16138999]
6. Chantada GL, Fandino A, Raslawski EC, et al. Experience with chemoreduction and focal therapy for intraocular retinoblastoma in a developing country. *Pediatr Blood Cancer*. 2005; 44:455–460. [PubMed: 15558702]
7. Rodriguez-Galindo C, Wilson MW, Haik BG, et al. Treatment of intraocular retinoblastoma with vincristine and carboplatin. *J Clin Oncol*. 2003; 21:2019–2025. [PubMed: 12743157]
8. Go RS, Adjei AA. Review of the Comparative Pharmacology and Clinical Activity of Cisplatin and Carboplatin. *Journal of Clinical Oncology*. 1999; 17:409. [PubMed: 10458260]
9. Egorin MJ, Van Echo DA, Tipping SJ, et al. Pharmacokinetics and dosage reduction of cis-diammine(1,1-cyclobutanedicarboxylato)platinum in patients with impaired renal function. *Cancer Res*. 1984; 44:5432–5438. [PubMed: 6386150]
10. Calvert AH, Egorin MJ. Carboplatin dosing formulae: gender bias and the use of creatinine-based methodologies. *European Journal of Cancer*. 2002; 38:11–16. [PubMed: 11750834]
11. Calvert AH, Newell DR, Gumbrell LA, et al. Carboplatin dosage: prospective evaluation of a simple formula based on renal function. *Journal of Clinical Oncology*. 1989; 7:1748–1756. [PubMed: 2681557]
12. Sculier JP, Paesmans M, Thiriaux J, et al. A comparison of methods of calculation for estimating carboplatin AUC with a retrospective pharmacokinetic-pharmacodynamic analysis in patients with advanced non-small cell lung cancer. *European Journal of Cancer*. 1999; 35:1314–1319. [PubMed: 10658520]
13. Ando M, Minami H, Ando Y, et al. Multi-Institutional Validation Study of Carboplatin Dosing Formula Using Adjusted Serum Creatinine Level. *Clinical Cancer Research*. 2000; 6:4733–4738. [PubMed: 11156227]

14. Jodrell DI, Egorin MJ, Canetta RM, et al. Relationships between carboplatin exposure and tumor response and toxicity in patients with ovarian cancer. *Journal of Clinical Oncology*. 1992; 10:520–528. [PubMed: 1548516]
15. Arant BS Jr. Postnatal development of renal function during the first year of life. *Pediatr Nephrol*. 1987; 1:308–313. [PubMed: 3153294]
16. Marina NM, Rodman J, Shema SJ, et al. Phase I study of escalating targeted doses of carboplatin combined with ifosfamide and etoposide in children with relapsed solid tumors. *Journal of Clinical Oncology*. 1993; 11:554–560. [PubMed: 8445431]
17. Murry DJ, Sandlund JT, Stricklin LM, Rodman JH. Pharmacokinetics and acute renal effects of continuously infused carboplatin. *Clin Pharmacol Ther*. 1993; 54:374–380. [PubMed: 8222479]
18. Rodman J, Maneval D, Magill L, Sunderland M. Measurement of Tc-99m DTPA serum clearance for estimating glomerular filtration rate in children with cancer. *Pharmacotherapy*. 1993; 13:10–16. [PubMed: 8437963]
19. Marina NM, Rodman JH, Murry DJ, et al. Phase I study of escalating targeted doses of carboplatin combined with ifosfamide and etoposide in treatment of newly diagnosed pediatric solid tumors. *J Natl Cancer Inst*. 1994; 86:544–548. [PubMed: 8133538]
20. Tonda ME, Heideman RL, Petros WP, Friedman HS, Murry DJ, Rodman JH. carboplatin pharmacokinetics in young children with brain tumors. *Cancer Chemother Pharmacol*. 1996; 38:395–400. [PubMed: 8765431]
21. Egorin MJ, Van Echo DA, Olman EA, Whitacre MY, Forrest A, Aisner J. Prospective Validation of a Pharmacologically Based Dosing Scheme for the cis-Diamminedichloroplatinum(II) Analogue Diamminecyclobutanedicarboxylatoplatinum. *Cancer Research*. 1985; 45:6502–6506. [PubMed: 3904984]
22. Chatelut E, Canal P, Brunner V, et al. Prediction of Carboplatin Clearance From Standard Morphological and Biological Patient Characteristics. *J Natl Cancer Inst*. 1995; 87:573–580. [PubMed: 7752255]
23. van Warmerdam LJC, Rodenhuis S, ten Bokkel Huinink WW, Maes RAA, Beijnen JH. Evaluation of formulas using the serum creatinine level to calculate the optimal dosage of carboplatin. *Cancer Chemother Pharmacol*. 1996; 37:266–270. [PubMed: 8529288]
24. Rodman JH, Maneval DC, Magill HL, Sunderland M. Measurement of Tc-99m DTPA serum clearance for estimating glomerular filtration rate in children with cancer. *Pharmacotherapy*. 1993; 13:10–16. [PubMed: 8437963]
25. Cockcroft W, Gault M. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976; 16:31–41. [PubMed: 1244564]
26. Jelliffe R. Estimation of Creatinine Clearance. *J Clin Pharmacol*. 2008; 48:1242–1244. [PubMed: 18812612]
27. Wright JG, Boddy AV, Highley M, Fenwick J, McGill A, Calvert AH. Estimation of glomerular filtration rate in cancer patients. *Br J Cancer*. 2001; 84:452–459. [PubMed: 11207037]
28. Schwartz GJ, Gauthier B. A simple estimate of glomerular filtration rate in adolescent boys. *J Pediatr*. 1985; 106:522–526. [PubMed: 3973793]
29. Shemesh O, Golbetz H, Kriss JP, Myers BD. Limitations of creatinine as a filtration marker in glomerulopathic patients. *Kidney Int*. 1985; 28:830–838. [PubMed: 2418254]
30. Ekhardt C, de Jonge ME, Huitema ADR, Schellens JHM, Rodenhuis S, Beijnen JH. Flat Dosing of Carboplatin Is Justified in Adult Patients with Normal Renal Function. *Clinical Cancer Research*. 2006; 12:6502–6508. [PubMed: 17085665]
31. Donahue A, McCune JS, Faucette S, et al. Measured versus estimated glomerular filtration rate in the Calvert equation: influence on carboplatin dosing. *Cancer Chemother Pharmacol*. 2001; 47:373–379. [PubMed: 11391850]
32. Dooley MJ, Poole SG, Rischin D, Webster LK. Carboplatin dosing: gender bias and inaccurate estimates of glomerular filtration rate. *European Journal of Cancer*. 2002; 38:44–51. [PubMed: 11750838]
33. Okamoto H, Nagatomo A, Kunitoh H, Kunikane H, Watanabe K. Prediction of carboplatin clearance calculated by patient characteristics or 24-hour creatinine clearance: a comparison of the

- performance of three formulae. *Cancer Chemother Pharmacol*. 1998; 42:307–312. [PubMed: 9744776]
34. Gaynon PS, Ettinger IJ, Moel D, et al. Pediatric phase I trial of carboplatin: a Children's Cancer Study Group report. *Cancer Treat Rep*. 1987; 71:1039–1042. [PubMed: 3315195]
 35. Newell DR, Pearson AD, Balmanno K, et al. Carboplatin pharmacokinetics in children: the development of a pediatric dosing formula. The United Kingdom Children's Cancer Study Group. *Journal of Clinical Oncology*. 1993; 11:2314–2323. [PubMed: 8246021]
 36. English MW, Skinner R, Pearson ADJ, Price L, Wyllie R, Craft AW. Dose-related nephrotoxicity of carboplatin in children. *Br J Cancer*. 1999; 81:336–341. [PubMed: 10496362]
 37. Madden T, Sunderland M, Santana VM, Rodman JH. The pharmacokinetics of high-dose carboplatin in pediatric patients with cancer. *Clin Pharmacol Ther*. 1992; 51:701–707. [PubMed: 1611808]
 38. Thomas H, Boddy AV, English MW, et al. Prospective Validation of Renal Function-Based Carboplatin Dosing in Children With Cancer: A United Kingdom Children's Cancer Study Group Trial. *Journal of Clinical Oncology*. 2000; 18:3614–3621. [PubMed: 11054434]
 39. Mann J, Raafat F, Robinson K, et al. The United Kingdom Children's Cancer Study Group's second Germ Cell Tumor study: carboplatin, etoposide, and bleomycin are effective treatment for children with malignant extracranial germ cell tumors, with acceptable toxicity. *J Clin Oncol*. 2000; 18:3809–3818. [PubMed: 11078494]
 40. Pinkerton CR, Broadbent V, Horwich A, et al. 'JEB' - A carboplatin based regimen for malignant germ cell tumours in children. *Br J Cancer*. 1990; 62:257–262. [PubMed: 1696831]
 41. Pein F, Michon J, Valteau-Couanet D, et al. High-dose melphalan, etoposide, and carboplatin followed by autologous stem-cell rescue in pediatric high-risk recurrent Wilms' tumor: a French Society of Pediatric Oncology study. *Journal of Clinical Oncology*. 1998; 16:3295–3301. [PubMed: 9779704]
 42. Kushner BH, Cheung N-KV, Kramer K, Dunkel IJ, Calleja E, Boulad F. Topotecan combined with myeloablative doses of thiopeta and carboplatin for neuroblastoma, brain tumors, and other poor-risk solid tumors in children and young adults. *Bone Marrow Transplant*. 2001; 28:551–556. [PubMed: 11607767]
 43. Liem RI, Higman MA, Chen AR, Arceci RJ. Misinterpretation of a Calvert-derived formula leading to carboplatin overdose in two children. *J Pediatr Hematol Oncol*. 2003; 25:818–821. [PubMed: 14528109]
 44. Chinnaswamy G, Cole M, Boddy AV, et al. Estimation of renal function and its potential impact on carboplatin dosing in children with cancer. *Br J Cancer*. 2008; 99:894–899. [PubMed: 18781149]

Figure 1.

Scatter plots showing the association between age at diagnosis and fixed per m² dose received/hypothetical Calvert dose (for patients who received fixed per m² doses during cycle 1) (n=54) (**A**); and the association between age at diagnosis and Calvert dose received/hypothetical fixed per m² dose (for patients who received Calvert doses during cycle 1) (n=40) (**B**).

Figure 2.
Profiles of GFR Values with Average Trend Line.

Table 1

Characteristics of study cohort (n=98)

	All patients	Method of carboplatin dosing				
N (%)		Fixed per m ²	Calvert	Calvert & Fixed per m ²	Fixed per kg	Calvert & Fixed per kg
No. of patients	98	50	32	14	1	1
Gender						
Male	55 (56)	30 (60)	15 (47)	9 (64)	0 (0)	1 (100)
Female	43 (44)	20 (40)	17 (53)	5 (36)	1 (100)	0 (0)
Race						
White	57 (58)	30 (60)	17 (53)	9 (64)	1 (100)	0 (0)
Black	25 (26)	13 (26)	8 (25)	4 (29)	0 (0)	0 (0)
Hispanic	15 (15)	7 (14)	6 (19)	1 (7)	0 (0)	1 (100)
Mixed	1 (1)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)
Laterality						
Bilateral	72 (73)	35 (70)	23 (72)	13 (93)	1 (100)	0 (0)
Unilateral	26 (27)	15 (30)	9 (28)	1 (7)	0 (0)	1 (100)
Age at diagnosis						
<1 year	66 (67)	26 (52)	24 (75)	14 (100)	1 (100)	1 (100)
≥1 –<2 years	24 (24)	18 (36)	6 (19)	0 (0)	0 (0)	0 (0)
≥2 –<4 years	7 (7)	5 (10)	2 (6)	0 (0)	0 (0)	0 (0)
>10 years	1 (1)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)

Table II

Summary statistics for cumulative doses of carboplatin received by dosing method

Method of Dosing	# of cycles	# of pts	Median	Minimum	Maximum	Mean	Std Dev
Calvert	0	1	.	.	.	.	.
	3	5	864.00	658.00	1143.00	907.60	185.27
	5	2	615.10	471.00	759.20	615.10	203.79
	6	13	1346.34	705.43	1986.00	1304.38	375.01
	7	2	1213.18	1112.85	1313.52	1213.18	141.89
	8	9	1104.10	779.00	1992.70	1221.53	413.06
	2	1	516.00	516.00	516.00	516.00	.
Fixed per m ²	3	1	699.00	699.00	699.00	699.00	.
	4	1	1013.00	1013.00	1013.00	1013.00	.
	5	5	1092.00	971.40	4652.00	1827.48	1590.63
	6	9	1814.40	1690.60	2066.20	1843.76	120.76
	7	6	1824.75	1405.00	2337.20	1821.30	377.25
	8	27	2151.80	1414.16	2852.00	2085.96	372.98

Table III
Differences in administered and hypothetical carboplatin doses and amounts per cycle

For cycles that used the modified Calvert Formula (per m ²):						
Variable	N	Median	Min	Max	Mean	SD
Calvert Fixed per m ² dose	259	-169.00	-292.00	190.00	-141.18	96.31
Calvert Fixed per m ² total amount	245	-64.00	-115.20	97.40	-53.41	37.67
Calvert Fixed per kg dose	n/a	n/a	n/a	n/a	n/a	n/a
Calvert Fixed per kg total amount	247	13.04	-36.31	185.84	24.25	41.22
Calvert/Fixed per m ² dose	259	69.8%	47.9%	133.9%	74.8%	17.2%
Calvert/Fixed per m ² total amount	245	71.0%	44.3%	134.1%	75.3%	17.5%
Calvert/Fixed per kg dose	n/a	n/a	n/a	n/a	n/a	n/a
Calvert/Fixed per kg total amount	247	109.4%	78.0%	195.7%	113.0%	22.8%
For cycles that used fixed per m ² dosing (per m ²):						
Fixed per m ² Calvert dose	398	45.39	-262.90	201.36	25.92	101.78
Fixed per m ² Calvert total amount	385	21.84	-173.66	140.29	7.42	51.69
Fixed per m ² Fixed per kg dose	n/a	n/a	n/a	n/a	n/a	n/a
Fixed per m ² Fixed per kg total amount	382	78.59	-184.46	113.72	66.04	35.88
Fixed per m ² /Calvert dose	398	108.8%	68.1%	156.1%	108.3%	19.8%
Fixed per m ² /Calvert total amount	385	107.6%	67.0%	175.9%	107.4%	19.7%
Fixed per m ² /Fixed per kg dose	n/a	n/a	n/a	n/a	n/a	n/a
Fixed per m ² /Fixed per kg total amount	382	139.2%	82.4%	177.1%	136.5%	16.5%
For cycles that used fixed per kg dosing (per kg):						
Fixed per kg Calvert dose	n/a	n/a	n/a	n/a	n/a	n/a
Fixed per kg Calvert total amount	6	-11.25	-11.28	-3.65	-9.86	3.06
Fixed per kg Fixed per m ² dose	n/a	n/a	n/a	n/a	n/a	n/a
Fixed per kg Fixed per m ² total amount	7	-82.60	-86.20	-75.00	-81.91	4.29

For cycles that used the modified Calvert Formula (per m ²):						
Variable	N	Median	Min	Max	Mean	SD
Fixed per kg/Calvert dose	n/a	n/a	n/a	n/a	n/a	n/a
Fixed per kg/Calvert total amount	6	93.0%	92.6%	97.6%	93.7%	1.9%
Fixed per kg/Fixed per m ² dose	n/a	n/a	n/a	n/a	n/a	n/a
Fixed per kg/Fixed per m ² total amount	7	63.4%	63.1%	70.7%	64.8%	2.8%

Table IV

Observed toxicity by carboplatin dosing method

	Calvert	Fixed per m ²	Fixed per kg
FN admission	20/260 7.7%	48/410 11.7%	0/7 0.0%
RBC transfusion	29/267 10.9%	46/410 11.2%	1/7 14.3%
PLT transfusion	11/267 4.1%	40/410 9.8%	1/7 14.3%
Delay[*]	83/224 37.1%	130/351 37.0%	0/6 0.0%

^{*}Time to the next course >25 days.

Abbreviations: FN: Fever and Neutropenia; RBC: Red Blood Cells; PLT: Platelets.

Table V

Results of models investigating hypothetical dose differences and dosing method as predictors of toxicity

	FN admission	RBC transfusion	Platelet transfusion	Delay *
Formula used Calvert Fixed per m ² **	P=0.114	P=0.896	P=0.013	P=0.878
Fixed per m² dose – hypothetical Calvert dose	P=0.633	P=0.107	P=0.003	P=0.652

* A cycle was considered delayed if the time to the next course was >25 days;

** Reference group.

Abbreviations: FN: Fever and Neutropenia; RBC: Red Blood Cells; PLT: Platelets.