Pharmacokinetics of Systemic Versus Focal Carboplatin Chemotherapy in the Rabbit Eye: Possible Implication in the Treatment of Retinoblastoma

Brandy C. Hayden,[1] *Maria-Elena Jockovich,*[1] *Timothy G. Murray,*[1] *Monika Voigt,*[1,2] *Peter Milne,*[1,3] *Martina Kralinger,*[1,4] *William J. Feuer,*[1] *Eleut Hernandez,*[1] *and Jean-Marie Parel*[1,5]

Purpose. To characterize the pharmacology and toxicity of intravenous versus focal carboplatin delivery in the rabbit eye.

Methods. Pharmacological distribution of carboplatin was examined in New Zealand White Rabbits after a single intravenous infusion of carboplatin (18.7 mg/kg of body weight), a single subconjunctival carboplatin injection (5.0 mg/400 μL), or a single application of carboplatin delivered by Coulomb-controlled iontophoresis (CCI; 14 mg/mL carboplatin, 5.0 mA/cm^2, 20 minutes). After each treatment, animals were euthanatized, and the eyes analyzed at 1, 2, 6, or 24 hours by atomic absorption spectroscopy to determine carboplatin concentration in ocular structures. Potential toxicity of focally delivered carboplatin was assessed by histology after six cycles of 5.0 mg carboplatin delivered by subconjunctival injection or six transscleral carboplatin CCI applications at 72-hour intervals (14.0 mg/mL, 20 minutes at 2.5 mA).

Results. Determination of concentrations through atomic absorption spectroscopy in the retina, choroid, vitreous humor, and optic nerve after subconjunctival injection or iontophoretic carboplatin delivery revealed significantly higher levels than those achieved with intravenous administration. Carboplatin concentrations in the blood plasma were found to be significantly higher after intravenous delivery than after focal delivery by subconjunctival injection or CCI. No evidence of ocular toxicity was detected after focally delivered Carboplatin.

Conclusions. Focal administration of carboplatin using subconjunctival or noninvasive CCI safely and effectively transmits this chemotherapeutic drug into the target tissues of the retina, choroid, vitreous, and optic nerve. These results suggest that focal carboplatin delivery may effectively increase intraorbital carboplatin concentrations while decreasing systemic exposure to this cytotoxic drug. (*Invest Ophthalmol Vis Sci.* 2004; 45:3644–3649) DOI:10.1167/iovs.04-0228

Advances in chemotherapeutic treatment agents for pediatric malignancies coupled with the ongoing concerns with globe-conserving external beam radiotherapy (EBRT) led several investigators to expand the application of systemic chemotherapy to the management of intraocular retinoblastoma.[1–4] Systemic chemotherapeutic delivery of carboplatin has become an essential component of solid-tumor treatment in pediatric oncology and has largely replaced EBRT as the primary treatment modality in patients with Reese-Ellsworth stage V bilateral retinoblastoma.[5–7] Systemic chemoreduction has been shown to decrease the size of intraocular retinoblastoma, allowing for more conservative, globe-preserving therapeutic treatment options.[4,8–10] Clinical studies have demonstrated that systemic carboplatin, coupled with local tumor therapy is an effective treatment option in children with retinoblastoma.[11–12]

Systemic chemotherapy, however, is associated with several potential, and real, concerns in its application in the treatment of childhood retinoblastoma. Systemic chemotherapy, like EBRT, may have the potential to increase the risk of delayed second cancers in childhood survivors with a germline mutation at the RB-1 gene. Systemic carboplatin chemotherapy is associated with significant morbidity and potential mortality through drug-related toxicities including neutropenia, bone marrow suppression, ototoxicity, nephrotoxicity, and central nervous system toxicity.[13–18]

Despite the improved therapeutic index achieved with carboplatin chemotherapy, systemic chemotherapy alone does not result in complete tumor control in most patients with retinoblastoma.[19,20] It has been hypothesized that incomplete tumor control may be associated with inadequate carboplatin penetrance into the ocular tissues, nontumoricidal intracellular levels within the retinoblastoma cells, or the selection of chemotherapy-resistant tumor cell lines. High intracellular carboplatin levels within tumor tissue is believed to be associated with increased tumor control and has prompted recent investigations of high-dose, focal chemotherapy protocols. Our laboratories have explored the efficacy and safety of focal chemotherapy for treatment in a transgenic murine model of retinoblastoma.[21–24]

Focal chemotherapy may afford patients the potential benefits associated with chemoreductive treatment and may spare patients the associated toxicities and widespread mutagenic potential of systemic delivery of chemotherapy. Focally delivered chemotherapy has the potential to have a significant impact on the management of human pediatric retinoblastoma. In the present study, we investigated an in vivo comparison of local, subconjunctivally injected, or iontophoretically administered carboplatin and systemic carboplatin treatment.

From the [1]Bascom Palmer Eye Institute, Department of Ophthalmology and the [3]Rosenstiel Marine School, University of Miami, Miami, Florida; the [2]Ophthalmic Clinic of Virchow/Charité Hospital, Humboldt University of Berlin, Berlin, Germany; the [4]Ophthalmic Clinic, University of Innsbruck, Austria, Innsbruck, Austria; and the [5]Department of Ophthalmology, University of Liège, Centre Universitaire Hospitalier Sart-Tilman, Liège, Belgium.

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Corresponding author: Timothy G. Murray, Bascom Palmer Eye Institute, P.O. Box 016880; Miami, FL 33101; tmurray@med.miami.edu.

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METHODS

The study protocol was approved by the University of Miami School of Medicine Animal Care and Use Review Board. All experiments in this study were conducted in accordance with the ARVO Statement for the Use of Animals in Ophthalmologic and Vision Research.

Thirty-six New Zealand White rabbits, 6 per time point and 12 for safety studies, with an average weight of 3.37 ± 0.33 kg were used in the study. Rabbits were anesthetized with intramuscular injections of ketamine hydrochloride (25 mg/kg) and xylazine hydrochloride (25 mg/kg) before all treatments. They were treated with intravenous or focal carboplatin chemotherapy, as indicated in the next section. Carboplatin doses were selected to reflect those previously used in human clinical treatments[25,26] and in studies performed in nonhuman primates.[27] Euthanasia was performed with intravenous injections of 390 mg pentobarbital sodium.

Subconjunctival Carboplatin Injections in Rabbit Eyes

Carboplatin (Paraplatin, $C_6H_{12}O_2PtO_4$; Bristol-Myers Squibb Pharmaceutical Research Institute, Hillsdale, NJ) solution was prepared immediately before injection by dissolving 5.0 mg carboplatin in 400 μL balanced salt solution. Carboplatin injections, at a total dose of 5.0 mg, were administered with a 30-gauge needle to the eye. Injections were administered at three injection sights in each eye (superior, superior nasal, and inferior subconjunctival space), using a total volume of 400 μL.

Coulomb-Controlled Iontophoretic Delivery of Carboplatin in Rabbit Eyes

Coulomb-controlled iontophoresis (CCI) was performed as previously described.[28–32] Carboplatin solution was prepared immediately before administration by dissolving the drug powder in balanced salt solution (pH 5.5). Carboplatin at a concentration of 14 mg/mL was administered in the transscleral CCI applicator. The custom-made conical transscleral probe for rabbits used in this study is fabricated of silicone elastomer (Med 6033; Nusil, Inc., Carpinteria, CA), with an annular surface of 0.5 cm^2 and an outer diameter of 17 mm, assuring its location between pars plana and limbus, with a clear opening of 13 mm to avoid contact with the cornea. CCI was applied for 20 minutes at a current density of 5 mA/cm^2. A peristaltic pump induced circulation and assured a constant drug flow. The transscleral applicator, containing the positively charged carboplatin solution, was the anode. A custom-made rectal probe served as the cathodal return electrode. Poor contact or accidental disruption of the circuit was indicated by an audiovisual alarm; and, as the instrument continuously recorded the total Coulombs delivered, a controlled and calibrated delivery of the drug was ensured. The battery-operated microprocessor programable CCI instrument produces a constant current (miliamperes) and uniform electrical field (volts per square centimeter) for the treatment duration (Fig. 1).

Intravenous Delivery of Carboplatin in Rabbit Eyes

Carboplatin solution was prepared immediately before injection, by dissolving 18.7 mg/kg carboplatin in balanced salt solution. A total volume of 60 mL was administered to the right ear vein at a flow rate of 1.0 mL/min.

Safety of Carboplatin Delivered by Subconjunctival Injections or CCI in Rabbit Eyes

Six animals received six serial subconjunctival carboplatin injections, at 72-hour intervals, at a dose of 5.0 mg in right eyes only, as just described. Six animals received six transscleral carboplatin CCI treatments at 72-hour intervals (14.0 mg/mL, 20 minutes at 2.5 mA) to right eyes only, as described earlier. Rabbits were euthanatized at 7 weeks after completion of the sixth carboplatin cycle. Eyes were immediately enucleated, immersed in 10% formalin, serially sectioned, stained with hematoxylin and eosin, and examined by light microscopy. Histopathologic evaluation was performed by a masked observer and graded for evidence of ocular toxicity. Photomicrographic studies were performed on optic nerve, retina, trabecular meshwork, and cornea to document anatomic status.

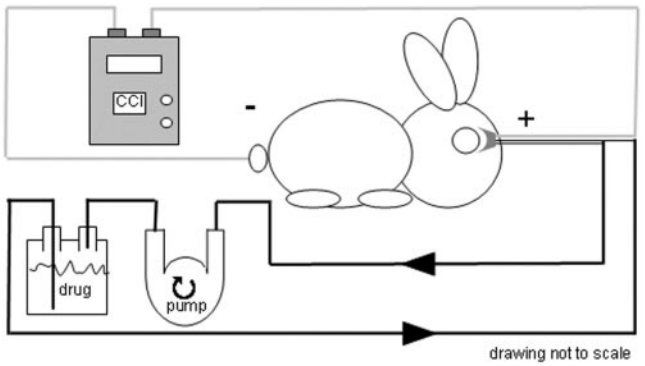


FIGURE 1. Line diagram of CCI delivery of carboplatin to the rabbit eye. CCI delivery of carboplatin was performed as depicted in the diagram. A peristaltic pump induced circulation and assured a constant drug flow. A transscleral applicator, containing the positively charged carboplatin solution, was the anode. A custom-made rectal probe served as the cathodal return electrode.

Tissue Dissection and Preparation

Six animals, six eyes per time point, were treated with either focal or intravenously delivered carboplatin, and eyes were enucleated at 1, 2, 6, or 24 hours after treatment and placed on ice. Animals receiving focal delivery either subconjunctivally or iontophoretically, were treated in the right eyes only. Left eyes were left untreated. All eyes were dissected, with sterile instruments used to isolate the retina, choroid, and optic nerve. Samples were frozen at −80°C and weighed. Tissues were freeze dried and dry weights recorded. All tissues were spiked with 20 μL of 16 M concentrated nitric acid (Fisher Scientific Laboratories, Fair Lawn, NJ) and 180 μL of 99.9% H_2O and centrifuged at 15,000 rpm for 20 minutes. At 8 hours, samples were diluted with 800 μL of 99.9% H_2O and centrifuged again. The supernatant was extracted and placed in vials for atomic absorption spectroscopy analysis.

Vitreous humor was aspirated with a 1.0 mL syringe and centrifuged for 20 minutes at 1700 rpm. Blood was drawn from an ear artery before enucleation. The blood was centrifuged at 1200 rpm for 10 minutes to isolate blood plasma. Samples (100 μL) were obtained, spiked with 20 μL of 16 M concentrated nitric acid (Fisher Scientific Laboratories) and 180 μL of 99.9% H_2O and centrifuged at 15,000 rpm for 20 minutes. At 8 hours, samples were diluted with 800 μL of 99.9% H_2O and centrifuged again. The supernatant was extracted and placed in vials for atomic absorption spectroscopy analysis.

Electrothermal Atomic Absorption Spectroscopy

Carboplatin, platinum metabolites, and protein conjugates were determined in ocular fluids and tissues as total acid soluble platinum (Pt) by electrothermal atomic absorption spectrometry (ET-AAS). ET-AAS has been used in previous pharmacokinetic studies of cisplatin[33] and has been demonstrated to be a valid method for the determination of platinum compounds in biological fluids.[34] This method determines total Pt in fluids or tissues, including any forms of the drug subject to hydrolytic action and subsequently inactivated by irreversible binding to protein and thus rendered inactive of cytotoxic effect.[35]

A Zeeman graphite furnace atomic absorption spectrophotometer (model 4100; Perkin Elmer Corp, Wellesley, MA) equipped with an autosampler and accompanying software (AAWinlab; Perkin Elmer) was used for the Pt concentration determinations. A Pt hollow-cathode

TABLE 1. Pharmacokinetic Distribution of Carboplatin in Target Tissues after Subconjunctival Injection, CCI, and Intravenous Administration

Treatment Modality	Time (h)	Retina (ng/mg)	Choroid (ng/mg)	Optic Nerve (ng/mg)	Vitreous (μg/mL)	Blood Plasma (μg/mL)
Subconjunctival	1	51.5 ± 22.1	612.4 ± 211.5	43.5 ± 16.6	4560.0 ± 1053.5	182.0 ± 452.1
Subconjunctival	2	53.7 ± 34.7	205.6 ± 86.2	30.0 ± 14.1	3305.0 ± 813.6	327.0 ± 21.2
Subconjunctival	6	10.2 ± 6.7	26.9 ± 7.0	13.9 ± 4.8	860.0 ± 56.1	75.0 ± 56.6
Subconjunctival	24	8.9 ± 8.3	18.5 ± 3.7	7.3 ± 1.1	1123.4 ± 176.5	14.0 ± 14.1
CCI	1	45.3 ± 36.0	483.2 ± 448.1	19.2 ± 13.1	1575.1 ± 850.4	260.9 ± 20.8
CCI	2	30.5 ± 28.3	155.1 ± 131.3	37.7 ± 48.1	1655.0 ± 1645.6	178.0 ± 43.3
CCI	6	4.5 ± 3.1	23.5 ± 23.8	7.1 ± 7.3	1955.0 ± 946.1	121.3 ± 36.0
CCI	24	1.9 ± 1.0	8.3 ± 36.0	3.9 ± 2.3	680.0 ± 205.4	103.0 ± 5.6
Intravenous	1	21.6 ± 9.4	47.8 ± 16.5	12.6 ± 3.1	331.7 ± 126.9	6222.7 ± 2554.9
Intravenous	2	18.4 ± 15.6	38.9 ± 30.4	24.0 ± 18.1	685.0 ± 276.8	3452.0 ± 1928.4
Intravenous	6	1.7 ± 0.8	14.6 ± 2.5	5.9 ± 2.1	1220.0 ± 1029.9	396.7 ± 66.6
Intravenous	24	0.001 ± 0.0	0.001 ± 0.001	0.001 ± 0.0	804.0 ± 1.0	8.0 ± 5.0

Data are the mean ± SD. The dose was a single injection of 5.0 mg/400μL; CCI was applied at 14 mg/mL, 7.5 mA/cm^2 for 20 minutes, and the intravenous carboplatin dose was 18.7 mg/kg body weight.

lamp emitting at 265.9 nm and at a low slit setting of 0.7 nm was used at the manufacturer's recommended current settings.

A total volume of 10 μL was introduced into the pyrolytically coated graphite tubes (Perkin Elmer). The tubes were routinely placed after a series of analytical runs (typically 150–200 firings). Each sample was analyzed in duplicate and the resultant absorbance readings averaged. Analytical standards (*cis*-diammine[1,1-cyclobutane-dicarboxylatol] platinum; Aldrich, Milwaukee, WI) at six levels of concentration were diluted in the same strength matrix acid (2% HNO_3) as the samples to establish a calibration. The temperature program used comprised a drying step (100°C, 30 seconds) and an ashing step (1300°C; 30 seconds), followed by atomization (2200°C, 6 seconds). The limit of detection of the analyses was better than 10 parts per billion (ppb; nanograms per milliliter). Samples with absorbance greater than the linear working range of the calibration curve (~ 3000 ppb) were quantitatively diluted and reanalyzed.

Statistical Analysis

Data were expressed in means and standard deviations. Carboplatin concentrations at all time points were analyzed and compared for each tissue, by using a general linear model in which carboplatin concentration was evaluated on a logarithmic scale to effect normality and homogeneity of variances. Treatment modality was an independent variable, and linear and quadratic components of time were included as covariates. Probabilities comparing treatment modalities reflect the difference in average concentration over the entire period studied (1–24 hours). Probabilities were not Bonferroni corrected, but because three treatment modalities were evaluated, the reader may consider 0.0167, rather than the usual 0.05, to indicate statistical significance.

RESULTS

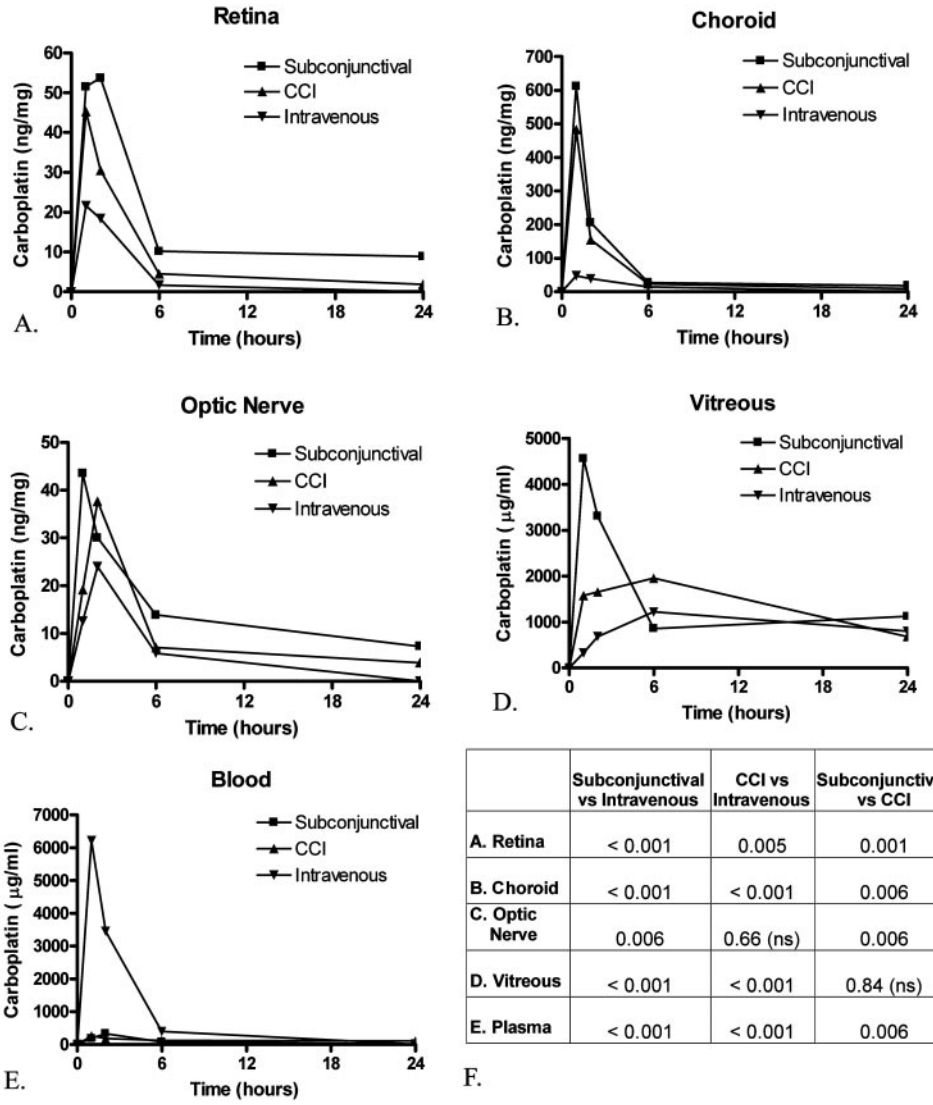
Histopathology indicated no toxicity in rabbit eyes after six serial subconjunctivally administered injections of carboplatin at doses of 5.0 mg or after six transscleral CCI applications (14 mg/mL carboplatin, 2.5 mA/cm^2, 20 minutes in duration/application) of carboplatin. With CCI, a slight transient conjunctival irritation that disappeared at postoperative day (POD) 1 was noted, but no corneal edema, tissue swelling, or other local complications occurred. Slight transient conjunctival irritation also occurred in the CCI control (no drug, no current). With subconjunctival injection a slight transient swelling of the conjunctiva that disappeared at POD 2 was observed. No signs of corneal irritation were detected.

Determination of concentrations by atomic absorption spectroscopy in the retina, choroid, vitreous, and optic nerve after subconjunctival injection or iontophoretic carboplatin delivery revealed significantly higher levels than those achieved with intravenous administration (Table 1, Fig. 2). Peak carboplatin levels in the retina were higher after subconjunctival injection (53.7 ng/mg) than after iontophoretic and intravenous delivery, with concentrations of 45.3 ng/mg and 21.6 ng/mg, respectively (Fig. 2A). Concentration versus time curves revealed statistically significant higher total levels of carboplatin in the retina over the 24-hour period after focal delivery than with intravenous injection (Fig. 2F). Peak levels of 612.4 ng/mg carboplatin in the choroid were obtained after subconjunctival injection, 483.2 ng/mg after iontophoretic delivery, and 47.8 ng/mg intravenous administration at 1 hour after delivery (Fig. 2B). Time course curves indicate carboplatin concentrations in the choroid after subconjunctival injection or CCI were significantly higher than those detected after intravenous injection (Fig. 2F). Peak concentrations in the optic nerve reached 43.5 ng/mg with subconjunctival injection, 37.7 ng/mg with iontophoretic delivery, and 24.0 ng/mg with intravenous administration (Fig. 2C). The concentration of carboplatin in the vitreous humor over time demonstrated differential pharmacokinetic distribution dependent on treatment administration. Concentrations in the vitreous after subconjunctival injection peaked at 1 hour (4560.0 μg/mL) and decreased thereafter. The drug concentration in the vitreous after iontophoretic administration was 1565.1 μg/mL at 1 hour and slowly increased to peak at 1955.0 μg/mL at 6 hours after treatment. Intravenous delivery of carboplatin resulted in a peak of 1220.0 μg/mL in the vitreous 6 hours after administration (Fig. 2D).

Carboplatin concentrations in the blood plasma were found to be significantly higher after intravenous delivery (6222.7 μg/mL at 1 hour) compared with subconjunctival (182.0 μg/mL at 1 hour) and iontophoretic (260.9 μg/mL at 1 hour) delivery. Blood plasma levels of carboplatin remained high up to 6 hours after intravenous delivery (Fig. 2E). Analyses of time course curves indicate carboplatin concentrations in the blood plasma after subconjunctival injection or CCI are significantly lower than those after intravenous injection (Fig. 2F).

DISCUSSION

Intravenous carboplatin chemotherapy is highly effective in reducing tumor volume in patients with Reese-Ellsworth stage IV or V bilateral retinoblastoma. Several investigators have reported on the effectiveness of initial intravenous chemotherapy, termed chemoreduction.[36–39] In a short-term study, Shields et al.[39] reported a mean decrease of 35% in tumor base and 49% in thickness in children initially treated with intravenous chemotherapy. Though effective in tumor reduction, this treatment modality alone does not achieve complete tumor control and thus requires adjuvant, focal treatment. Chemore-



	Subconjunctival vs Intravenous	CCI vs Intravenous	Subconjunctival vs CCI
A. Retina	< 0.001	0.005	0.001
B. Choroid	< 0.001	< 0.001	0.006
C. Optic Nerve	0.006	0.66 (ns)	0.006
D. Vitreous	< 0.001	< 0.001	0.84 (ns)
E. Plasma	< 0.001	< 0.001	0.006

F.

FIGURE 2. Time course of carboplatin concentration in various ocular tissues. Comparison of carboplatin concentrations after subconjunctival injection, CCI, or intravenous administration in the retina (**A**), choroid (**B**), optic nerve (**C**), vitreous (**D**), and blood plasma (**E**). Carboplatin concentrations at all time points were analyzed and compared for each tissue. Probabilities comparing treatment modalities reflect the average difference over the entire time period studied (1–24 hours) (**F**).

duction combined with local therapies including laser hyperthermia and cryoablative therapy have been used with much success.[1,3,8,40] However, seeding of cancer cells into the vitreous humor remains a problem in patients treated with these combined therapies. It appears that insufficient concentrations of the chemotherapeutic drug are achieved in the retina and vitreous through intravenous administration. Dose limitations and rapid renal clearance of the drug may also be contributing factors.

Previous studies in our laboratory have demonstrated the efficacy of carboplatin administered intravitreally, subconjunctivally, and iontophoretically in the treatment of murine retinoblastoma (Hayden BC, et al. *IOVS* 2000;41:ARVO Abstract 4178).[21,23,24,41] Although efficacious, direct injection into the vitreous cavity creates the possibility of tumor dissemination from the injection tract, may increase the risk of extraocular metastasis, and therefore is not used in clinical practice. Subconjunctival and iontophoretic focal delivery of carboplatin may deliver high-dose chemotherapy to the vitreous and posterior segments of the eye without the risks associated with globe penetration.

Iontophoresis uses a low-potential, continuous electrical field incorporating two conductive electrodes to transfer ions across a tissue barrier. In the past 10 years, numerous studies have documented the delivery of various drugs into ocular tissues in both the anterior and posterior with various degrees of success.[28–32,42–45] The CCI system used in this study is specifically designed for ophthalmic application and is in clinical use in Europe.[46,47] The system used maintains a constant current density, a constant concentration of carboplatin, and a constant suction throughout the treatment period. This results in effective transmission of drug into the ocular tissues without high charge density and fluctuation, thus reducing complications such as tissue burning. Although the exact mechanism of action is unknown, it is postulated that the electrical field alters the epithelial interstitial spaces, allowing the ionized drug to transfer across the treatment tissue.[42] When iontophoresis is used for drug delivery, the best candidate drug is a low molecular weight, charged molecule. Carboplatin, a crystalline powder with a low molecular weight with a positive charge when dissolved in balanced salt solution, is uniquely attractive for application of CCI in the treatment of retinoblastoma.

Results from this study suggest that focal delivery of carboplatin using subconjunctival injection or iontophoretic delivery transmits drug more effectively than intravenous delivery into the target tissues of the vitreous, choroid, retina, and optic nerve in the rabbit eye. Both focal applications resulted in significantly higher peak concentrations of carboplatin in the choroid, retina, optic nerve, and vitreous than those obtained after intravenous delivery. Focal chemotherapeutic delivery resulted in dramatically decreased carboplatin levels in the blood plasma compared with intravenous delivery.

Locally administered carboplatin resulted in high concentrations of the drug in the vitreous humor, which may be of clinical importance in the treatment of human retinoblastoma. Peak levels of 4560.0 μg/mL after subconjunctival carboplatin injection (5.0 mg) and 1955.0 μg/mL after iontophoretic delivery (14 mg/mL) were found in the vitreous humor. These carboplatin levels in the vitreous reported in the present study compare well with those reported by Mendelsohn et al.[27] in a recent primate study of ocular pharmacokinetics of carboplatin. In this latter study, similar carboplatin levels in the vitreous humor were measured after peribulbar or episcleral local delivery of carboplatin. Peak vitreous levels were 2380 μg/mL (10.0 mg carboplatin) and 2950 μg/mL (10.0 mg carboplatin) with peribulbar administration and episcleral balloon delivery, respectively.

The pharmacokinetics of carboplatin obtained in the vitreous after CCI resulted in a distinctly different pattern of drug distribution than observed after subconjunctival injection. Carboplatin levels peaked at 1 hour after subconjunctival delivery and slowly diminished thereafter. The distribution in the vitreous after iontophoretic delivery demonstrated heightened levels of carboplatin from 1 to 6 hours with peak levels at 6 hours after treatment. The ability to deliver carboplatin in a controlled, sustained manner to the vitreous may have significant clinical value. Current clinical treatment failures of children receiving primary systemic chemotherapy for retinoblastoma often fail due to proliferation of cancerous cells seeded in the vitreous.[19] We hypothesize that this may be secondary to insufficient carboplatin penetration. Noninvasive iontophoretic delivery of the drug may therefore be the preferential treatment for children displaying vitreous seeding at treatment onset. Subconjunctival therapy may be most useful in large tumor where it is necessary to rapidly reduce tumor size with frequent chemotherapy treatment cycles.

Systemic administration of carboplatin has also been evaluated in children undergoing enucleation management of intraocular retinoblastoma. In this study, Murphree et al.[1] noted intratumoral concentrations of carboplatin to be 2.2 pg/μg DNA. These levels are lower than those reported in the present study.

Peak levels of carboplatin detected in the blood plasma after focal administration were dramatically less than those achieved after intravenous administration of carboplatin. Clinically, this has profound implications. Systemic chemotherapy is an effective treatment option in the treatment of children with retinoblastoma and results in a reduction in tumor size, enhanced efficacy of other treatment modalities, and the possible prevention of micrometastasis. However, serious complications still exist.[18,48] Systemic chemotherapy has been associated with myelosuppression, nephrotoxicity, ototoxicity, and sepsis, and may increase the risk of acute nonlymphatic leukemia and other secondary malignancies later in life.[16,18,48,49] Previous experiments in our laboratory indicate that focal carboplatin delivery (subconjunctival injection or CCI) minimize concerns associated with morbidity in the treatment of murine retinoblastoma.[41] A phase I/II clinical trial for the evaluation of the efficacy and toxicity of subconjunctival carboplatin for intraocular retinoblastoma showed that this treatment modality is promising, although further studies are required.[26]

Subconjunctival delivery of carboplatin is able to enhance the efficacy of other treatment modalities in the treatment of murine retinoblastoma.[41] The most effective and least toxic combination therapy for the treatment of human pediatric retinoblastoma appears to be the utilization of subconjunctivally or iontophoretically administered carboplatin in addition to other local treatments such as laser hyperthermia/photoablation, cryoablation, or radiotherapy. Several clinical studies indicate systemic chemotherapy may be most valuable as a treatment for retinoblastoma when it is combined with local treatment strategies to enhance efficacy.[4,8,50] A cocktail of carboplatin, vincristine, and etoposide administered systemically with cyclosporine after a session of cryotherapy and focal ablation has been shown to be highly effective in treating retinoblastoma in children.[3,51]

The results of the present study, demonstrating increased intraocular concentrations of carboplatin after local delivery compared with systemic delivery, indicate that local chemotherapy combined with other local treatments may be more successful and less toxic than current combined regimens. Future studies will focus on the pharmacokinetics of carboplatin combined with other treatment modalities.

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