



RETINAL TUMORS

Retinal neovascularization associated with retinoblastoma

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PURPOSE: To report retinal neovascularization associated with retinoblastoma in a 14-month-old infant.

DESIGN: Observational case report.

METHODS: Review of clinical and pathologic findings.

RESULTS: A large frond of retinal neovascularization was present posterior to the lens in the right eye, which also contained a retinoblastoma.

CONCLUSIONS: Retinal neovascularization is an unusual association with retinoblastoma.

Hereditary cancer predisposition syndromes

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Cancer genetics is increasingly becoming integrated into the practice of modern medical oncology. The ability to distinguish a growing proportion of the 5% to 10% of all cancers that develop in individuals who have inherited a genetic mutation conferring heightened susceptibility to specific cancers may permit targeted efforts in cancer surveillance and prevention. While these individuals comprise a small proportion of the overall burden of cancer, strategies successful in reducing their remarkable cancer risks may be generalizable to the broader population. In this review, we highlight the most common hereditary cancer syndromes, most attributable to genes inherited in an autosomal dominant manner with incomplete penetrance, and a number of rare syndromes in which particular progress has been made. The prevalence, penetrance, tumor spectrum, and underlying genetic defects are discussed and summarized in a large table in which a more comprehensive enumeration of syndromes is provided.

Human retinoblastoma cells are resistant to apoptosis induced by death receptors: role of caspase-8 gene silencing.

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PURPOSE: Fas ligand (FasL) and TNF-related apoptosis-inducing ligand (TRAIL)/Apo2L are members of the TNF α family that can trigger apoptosis in susceptible cells via respective death receptors (DRs). FasL cross-links its receptor Fas, resulting in recruitment and proteolytic activation of caspase-8, which initiates the downstream apoptotic cascade. TRAIL signals through its receptors DR4 and DR5, which can activate caspase-8 as well. This study was undertaken to investigate the functional status of the FasL and TRAIL apoptotic pathways in retinoblastoma (Rb) cells.

METHODS: The human Rb cell lines Y79 and WERI-Rb1 were evaluated for their response to the Fas cross-linking antibody CH11 and recombinant TRAIL, as well as for cell surface presence and mutational status of Fas, DR4, and DR5 by flow cytometry and genomic DNA sequencing, respectively. The expression of caspase-8 and its inhibitor FLIP, as well as their recruitment to the DR signaling complex were studied by immunoblot analysis.

RESULTS: Rb cells express Fas, DR4, and DR5 on their surfaces, yet were resistant to DR-mediated apoptosis. This was not due to DR mutations or secretion of the soluble decoy Fas, antiapoptotic NF- κ B activity, or FLIP overexpression, but to the absence of caspase-8 expression. The demethylating agent 5-aza-2'-deoxycytidine restored caspase-8 expression and sensitivity to DR-mediated apoptosis.

CONCLUSIONS: Rb cells are resistant to DR-mediated apoptosis because of a deficiency in caspase-8 expression secondary to epigenetic gene silencing by overmethylation. The data help delineate the apoptotic pathways in Rb cells and suggest that the combination of demethylating agents with DR-activating modalities, such as TRAIL receptor monoclonal antibodies, may benefit patients with retinoblastoma.

Combretastatin A-4 prodrug in the treatment of a murine model of retinoblastoma

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PURPOSE: To evaluate the effect of subconjunctival injections of combretastatin A-4 phosphate (CA-4P) prodrug treatment on tumor vasculature and growth in an animal model of hereditary retinoblastoma.

METHODS: Twenty-four, 12-week-old simian virus-40 T-antigen-positive mice received six subconjunctival CA-4P injections at doses of 0.5, 1.0, 1.5, and 2.0 mg delivered at 72-hour intervals to the right eye only. Six control animals received placebo treatment. All animals underwent serial ophthalmic evaluations and were euthanized at 16 weeks of age, and eyes were obtained for histopathologic examination. Eyes were graded for presence or absence of tumor, delay of tumor growth, and intratumoral vascularity.

RESULTS: The use of subconjunctivally injected CA-4P prodrug induced an extensive, dose-dependent decrease in microvessel density and led to significant tumor reduction in treated eyes compared with the placebo control ($P < 0.001$). No evidence of corneal, lenticular, choroidal, or retinal toxicity was observed by histopathologic evaluation.

CONCLUSIONS: Subconjunctival delivery of CA-4P is associated with extensive dose-dependent reduction in blood vessel count in this murine model of retinoblastoma. A combination treatment of retinoblastoma incorporating CA-4P may allow enhanced tumor reduction enabling a decrease in standard treatment doses of both chemotherapy and external beam radiotherapy.

Optical coherence tomography in children: analysis of 44 eyes with intraocular tumors and simulating conditions

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PURPOSE: To investigate the role of optical coherence tomography (OCT) in the evaluation of fundus tumors and simulating lesions in children.

PATIENTS AND METHODS: We report the results of a retrospective single-center case series of 44 eyes of 44 children younger than age 18 with fundus lesions who were evaluated with OCT. In comparison, 12 eyes of 12 children with a normal macula were evaluated with OCT. Main outcome measures were cooperation of children while undergoing OCT and correlation of OCT findings with clinical and ultrasonographic findings

RESULTS: The OCT was performed without difficulty in all 56 children. Mean patient age was 12 years (median, 12 years; range, 4 to 17 years). The mean horizontal foveal thickness in the 12 normal eyes was 137 microm (median, 132 microm; range, 109 to 185 microm). Clinical diagnoses included retinoblastoma in 10 (23%) eyes, Coats' disease in 4 (9%) eyes, retinal capillary hemangioma in 3 (7%) eyes, astrocytic hamartoma of the retina in 3 (7%) eyes, toxocara granuloma in 2 (5%) eyes, and others. OCT was more sensitive than clinical examination in detection of macular pathology including shallow posterior vitreous detachment, surface wrinkling maculopathy, cystoid and noncystoid macular edema, subfoveal fluid, and retinal thinning. In comparison to ultrasonography, OCT was more sensitive in detection of surface wrinkling maculopathy, macular edema, and subfoveal fluid. Ultrasonography was more sensitive in detection of posterior vitreous detachment.

CONCLUSIONS: OCT is a useful and well-tolerated diagnostic modality for macular evaluation in children. It is more sensitive than clinical examination and ultrasonography in the detection of surface wrinkling maculopathy, macular edema, and subfoveal fluid.

Management of porous polyethylene implant exposure in patients with retinoblastoma following enucleation

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Ophthalmic Surg Lasers Imaging. 2004 Nov-Dec;35(6):446-52

BACKGROUND AND OBJECTIVE: To report the features and the management of porous polyethylene implant exposure in patients with retinoblastoma following enucleation.

PATIENTS AND METHODS: The medical records of 33 patients (33 sockets) following enucleation and porous polyethylene implantation for retinoblastoma were reviewed.

RESULTS: The mean age at enucleation was 24 months (range, 2 to 85 months). The exposure rate was 33% (11 cases), and the mean time from enucleation to exposure was 15 months (range, 7 to 29 months). One case was resolved only by supportive management, and the remaining 10 were successfully treated with a scleral patch graft and maintained well during a mean follow-up of 15 months after surgical repair. There was no statistical evidence that age, gender, implant size, or chemotherapy had an effect on implant exposure.

CONCLUSIONS: Porous polyethylene implant exposure does not seem to be resolved by conservative

management. We recommend early surgical management, such as scleral patch graft, as opposed to supportive management.

Systemic melanoma metastatic to the retina and vitreous

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PURPOSE: Report of a case of retinal and vitreous metastases of a systemic melanoma, possibly arising in the lung, that responded favourably to radiotherapy.

CASE REPORT: Retinal and vitreous metastases were demonstrated in a 57-year-old woman during routine follow-up after surgical resection of a melanoma presumed to be a primary pulmonary melanoma. After a 7-week observation period, which confirmed the progressive nature of the intra-ocular lesions, the patient was treated by external beam radiotherapy at a dose of 35 Gy delivered in 14 fractions of 2.5 Gy. Complete disappearance of the vitreous invasion and progressive elimination of the retinal invasion were observed over a period of 9 months. Final visual function was 20/25.

REVIEW OF PUBLISHED CASES: A review of the literature identified 28 cases of melanoma with metastases to the retina and vitreous. In almost all of these cases, the primary tumour was a cutaneous melanoma and the mean patient survival following the diagnosis of intra-ocular metastases was 22 months. Retinal metastases, as in the case reported here, present a vascular tropism and tend to develop around veins. These metastases are generally unilateral and may be either solitary or multiple. Tumour invasion of the vitreous occurred by means of isolated cells forming a suspension of aggregates or spherules. Vitreous haemorrhage and irreducible neovascular glaucoma leading to functional impairment, which requires enucleation, were both the most frequent and the most serious complications of these metastases. Treatment is always palliative and is effective in cases with limited retinal and vitreous invasion, as in the case reported here.

CONCLUSIONS: Metastatic melanoma in the retina and vitreous is a rare entity and can lead to functional impairment and enucleation because of neovascular glaucoma. As treatment is only effective in cases with limited invasion, systematic screening is recommended in all patients with a metastatic cutaneous melanoma presenting with suggestive ocular symptoms.

EpCAM expression in retinoblastoma: a novel molecular target for therapy

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PURPOSE: This study was conducted to investigate the potential of targeting epithelial cell adhesion molecules (EpCAMs) in the treatment of retinoblastoma. It was first determined whether EpCAM is expressed in retinoblastoma and then whether EpCAM reactivity correlates with tumor aggressiveness.

METHODS: EpCAM reactivity was evaluated by immunohistochemistry in 43 retinoblastoma specimens from 43 patients, by using the monoclonal antibody GA733.2. The tumors were divided into two groups. There were 20 tumors with no invasion of the choroid and optic nerve (group A) and 23 tumors with invasion of the choroid, optic nerve, and orbit (group B). EpCAM reactivity was correlated with invasion

and differentiation of the tumors.

RESULTS: Among the 43 tumors, EpCAM reactivity was observed in 100% (43/43) tumors. EpCAM reactivity was significantly higher in the invasive than the noninvasive tumors ($P < 0.05$) and in poorly differentiated than in well-differentiated tumors ($P < 0.005$). Non-neoplastic retina also expressed EpCAM.

CONCLUSIONS: The results confirm that EpCAM is vastly expressed in retinoblastoma and point to its use as a target for therapy in the future.

Second primary myogenic sarcoma in a patient with bilateral retinoblastoma

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Retinoblastoma is the primary ocular malignancy affecting children under 6 years of age. The development of second malignant tumors in survivors of hereditary retinoblastoma is a well-known clinical entity and a major cause of morbidity and mortality. Rhabdomyosarcomas as second primary tumors have been only rarely described. The authors report a patient with bilateral retinoblastoma who developed a myogenic sarcoma of the orbit after 5.5 years of diagnosis. The short latency period may be explained by tumor histology with the contribution of radiotherapy and chemotherapy. The prognosis of second tumors is poor despite aggressive treatment.

Multidrug resistant proteins: P-glycoprotein and lung resistance protein expression in retinoblastoma

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BACKGROUND/AIM: Retinoblastoma is the commonest primary intraocular tumour in children. Chemotherapy now plays a big part in the treatment of these tumours. There is not much information about the role of the multidrug resistance proteins (MDR)-P-glycoprotein (P-gp) and vault protein lung resistance protein (LRP)-in retinoblastoma. The authors investigated the expression of P-gp and LRP in retinoblastoma and correlated them clinicopathologically.

METHODS: Among 60 retinoblastomas, 40 tumours were not subjected to preoperative or postoperative chemotherapy and 20 tumours were subjected to postoperative chemotherapy. In this cohort 27 tumours had no invasion and 33 tumours had invasion of choroid, optic nerve, and orbit. P-gp and LRP expression were studied by immunohistochemistry. Immunoanalysis was done semiquantitatively.

RESULTS: Among the 60 tumours P-gp was expressed in 23 (38%) tumours and LRP was expressed in 35 (58%). P-gp was expressed in 11/27 (40%) tumours with no invasion and in 12/33 (36%) tumours with invasion. LRP was expressed in 15/27 (55%) tumours with no invasion and in 20/33 (60%) tumours with invasion. Both P-gp and LRP were negative in three tumours with invasion, which had later developed bone marrow metastasis. There was no correlation between P-gp and LRP expression with invasion, differentiation and laterality of the tumours and response to treatment.

CONCLUSION: Retinoblastoma expresses P-gp and LRP intrinsically before chemotherapy and none of these proteins predicted the response to chemotherapy. Thus, further studies are needed to understand the significance of the expression of the P-gp and LRP proteins in retinoblastoma.

Nm23 expression in retinoblastoma

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PURPOSE: Nm23 is a metastasis-suppressor protein. Decreased nm23 protein contributes to aggressiveness in many tumors. Nm23 immunoreactivity was studied in retinoblastoma and correlated with differentiation and invasiveness.

METHODS: Immunohistochemistry was performed on 73 formalin-fixed, paraffin-embedded specimens of retinoblastoma. Western blot was conducted to confirm the immunohistochemical study. Prognostic features such as differentiation, invasion of choroid, optic nerve, and orbit, and metastasis were analyzed.

RESULTS: Intense nm23 immunoreactivity was seen in 61% of the retinoblastomas with no invasion and faint nm23 immunoreactivity was seen in 85% of the retinoblastomas with invasion ($p < 0.001$). Poorly differentiated retinoblastoma showed decreased nm23 immunoreactivity compared to well-differentiated retinoblastomas ($p = 0.02$). An inverse correlation was observed between invasion of choroid, optic nerve, orbit, and metastasis, and nm23 immunoreactivity. Western blot assays of fresh tumor extracts confirmed the immunohistochemical findings.

CONCLUSIONS: Decreased nm23 immunoreactivity was seen in poorly differentiated retinoblastomas and in retinoblastomas with invasiveness. These findings may lay the groundwork for further studies to better understand the molecular mechanisms and provide a more accurate prediction of invasion and metastasis of retinoblastoma.

Evaluation of the antitumor effects of Herpes simplex virus lacking ribonucleotide reductase in a murine retinoblastoma model

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PURPOSE: To determine if an attenuated herpes simplex virus (HSV) lacking the large subunit of ribonucleotide reductase has antitumor effects in a transgenic mouse model of retinoblastoma (LHbetaTAg).

METHODS: LHbetaTAg mice were injected ocularly with 1×10^6 pfu of the hrR3 virus and tumor sizes were measured 3 weeks later. Replication of the virus in the eye and cultured murine retinoblastoma cells was tested by titration. Distribution of the virus in tumor was measured by X-gal staining.

RESULTS: Intraocular injection of mice with hrR3 ($n = 24$) did not result in a significant reduction in tumor size compared to uninjected ($n = 24$) or PBS injected controls ($n = 16$). Neither the hrR3, nor the HSV RE6 mutant, which was previously shown to have antitumor effects in vivo, replicated in cultured murine tumor cells in vitro, compared to wild-type HSV. The hrR3 virus also did not replicate significantly in tumor cells in vivo, compared to normal eye tissue.

CONCLUSIONS: These results suggest that mutant HSV lacking ribonucleotide reductase do not display oncolytic activity in the LHbetaTAg mouse and that this model may not be suitable for studying viral oncolysis as a therapy for retinoblastoma.

Visual recovery after radiation therapy for bilateral subfoveal acute myelogenous leukemia (AML)

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PURPOSE: Present a case of bilateral foveal acute myelogenous leukemic tumors that responded to radiation therapy. **DESIGN:** Case report.

METHODS: A patient was diagnosed with bilateral subfoveal infiltration of known systemic acute myelogenous leukemia. He received a standard induction chemotherapy, followed by consolidation therapy for his systemic leukemia. However, despite a complete marrow response, the intraocular tumors did not regress. Therefore, he was given low dose (1950-cGy) ocular external beam radiation therapy.

RESULTS: One course of systemic cytarabine chemotherapy failed to control the subfoveal tumors, leaving the patient at risk for permanent vision loss. In contrast, external beam radiation therapy improved his vision from 20/60 in his right eye to 20/20 and from 20/70 in his left eye to 20/25.

CONCLUSION: Although systemic chemotherapy can be used to treat intraocular metastasis, external beam radiation may provide more prompt resolution of vision-threatening tumors.

Second primary osteosarcoma with rosette-like structure in a patient with retinoblastoma

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A Japanese male patient developed bilateral retinoblastomas at the age of 1 year, but remained continuously disease-free after enucleation of the left eye and radiation therapy to the right eye. He noticed a painless hard mass around the right temporal bone when he was 25 years old. Biopsy specimen showed a small multi-nodular proliferation of tumor cells with prominent rosette-like structures. Eosinophilic material with focal mineralization was seen in the center of the rosettes. Immunostaining of the tumor cells showed positive reactions for epithelial membrane antigens CD 56 and CD 99. The patient was treated with systemic chemotherapy, and the tumor partially diminished. It is well known that a few osteosarcomas show a rosette-like appearance with production of osteoid in the center, but this is the first case of second primary osteosarcoma with prominent rosette-like features.

Solitary retinal astrocytoma in an infant

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A 5-month-old infant presented with a solitary retinal astrocytoma that clinically and ultrasonographically mimicked retinoblastoma. The diagnosis was established on histopathologic examination. There was no

systemic evidence of tuberous sclerosis or neurofibromatosis. Thus, solitary, large, retinal astrocytomas can occur in the absence of any systemic manifestations.

Detection of germline mutations in argentine retinoblastoma patients: low and full penetrance retinoblastoma caused by the same germline truncating mutation

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Constitutional RB1 gene mutations were studied in a series of 21 families with unilateral and bilateral retinoblastoma patients. Peripheral blood lymphocytes were analyzed by "exon by exon" PCR-heteroduplex and sequencing. Mutations were identified in 6 (29%) of the patients. One mutation corresponded to an intronic polymorphism in g.174351T > A. The other five mutations resulted C to T exonic transitions, four were CGA sequences (g.65386, g.150037 in two patients, and g.162237), creating stop codons and presumably truncated proteins. The fifth one was new and resulted in alanine to valine substitution (g.73774). Two patients had the same germline truncated mutation (g.150037C > T), one with a familial bilateral early onset retinoblastoma and one with a sporadic unilateral late onset retinoblastoma. The later type has not been previously described. This finding is discussed in the genotype/phenotype correlation context. Additionally, a single nucleotide change was found in six studied samples, where a C to T homozygous transversion was identified in intron 26 (IVS26 + 28). It is worthy the non concordance of the nucleotide with the published sequence. This analysis proved to be a useful method for the detection of mutations in the RB1 gene, and contributed to the adequate genetic counseling to patients and relatives.

Causes of chemoreduction failure in retinoblastoma and analysis of associated factors leading to eventual treatment with external beam radiotherapy and enucleation

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PURPOSE: To evaluate the causes of chemoreduction failure in retinoblastoma and to analyze the associated factors for eventual treatment with external beam radiotherapy and enucleation.

DESIGN: Prospective noncomparative case series.

PARTICIPANTS: Seventy-one patients with 105 eyes with intraocular retinoblastoma that underwent chemoreduction therapy between October 1998 and January 2003.

INTERVENTION: A 6-treatment cycle of chemoreduction therapy with vincristine, etoposide, and carboplatin was administered at monthly intervals. Unresponsive disease was defined as persistence of retinal tumors, vitreous seeds, or subretinal seeds after the second treatment cycle, with no appreciable sign of regression. Eyes with unresponsive disease were enucleated after the second treatment. Eyes that responded to chemoreduction therapy received focal treatment, including indirect laser photocoagulation, transpupillary thermotherapy, cryotherapy, and ruthenium 106 episcleral plaque radiotherapy after the second chemoreduction treatment, if necessary, to achieve complete tumor regression. Recurrence was defined as the regrowth of retinal tumors, vitreous or subretinal seeds after an initial favorable response, and regression. Recurrent retinal tumor, vitreous seeds, or subretinal seeds were treated with focal treatments and 2 to 3 additional chemoreduction treatments. When these

methods failed or were not applicable, external beam radiotherapy and/or enucleation was administered.

MAIN OUTCOME MEASURES: The use of external beam radiotherapy and enucleation for chemoreduction failure, which was defined as unresponsive or recurrent disease.

RESULTS: The mean follow-up was 25.7 months (range: 6-49). Ten of 105 eyes (9.5%) with unresponsive disease were enucleated after the second treatment. Of the remaining 95 eyes, 42 (44.2%) developed recurrence after chemoreduction. Recurrent disease failing to be treated successfully by other methods was treated with external beam radiotherapy in 26 of 95 eyes (27.4%) and enucleation in 22 of 95 eyes (23.2%). External beam radiotherapy was successful in preventing enucleation in 20 of 26 eyes (76.9%). Overall, the globe salvage rate was 69.5%, ranging from 36.1% for Reese-Ellsworth group V disease to 87.0% for groups I to IV disease. Histopathologically, 29 of 31 enucleated eyes (93.5%) had poorly differentiated or moderately differentiated retinoblastoma. Using multivariate logistic regression analysis, factors predictive of eventual treatment with external beam radiotherapy were female gender ($P = 0.010$), presence of subretinal seeds ($P = 0.023$), and a greater number of chemoreduction treatments ($P = 0.027$). By multivariate analysis, the factors associated with the need for eventual treatment with enucleation were recurrence of retinal tumors ($P = 0.004$), presence of vitreous seeds ($P = 0.008$), greater tumor thickness ($P = 0.015$), presence of subretinal fluid ($P = 0.040$), and older patient age ($P = 0.042$).

CONCLUSIONS: Chemoreduction failure in this article was defined as unresponsive or, more commonly, recurrent retinoblastoma. Older patient age, greater tumor thickness, presence of vitreous seeds and subretinal fluid at baseline, and retinal tumor recurrence after chemoreduction were factors associated with the need for enucleation.

Genetic diagnosis of retinoblastoma by a combination of fluorescence in situ hybridization and restriction fragment length polymorphism

[Article in Japanese]

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PURPOSE: It is important to exclude germ line mutation in cases of unilateral retinoblastoma(RB) to estimate hereditary or possible secondary cancer. We investigated whether genetic diagnosis is feasible in a health check screening program.

METHODS: Five patients with RB had surgery for enucleation in Keio University Hospital. Tumor cells from enucleated eyes and lymphocytes representing systemic cells were collected and analyzed genetically by fluorescence in situ hybridization(FISH) and restriction fragment length polymorphism (RFLP).

RESULTS: One out of three unilateral RB cases could be diagnosed as non-hereditary by the finding of no copies of the RB gene in the tumor cells using the FISH method and no signal in the RFLP method. A decrease of signal in tumor cells to less than 50% in the RFLP method was observed in another case of unilateral RB that seemed to be non-hereditary, but the case ultimately could not be diagnosed as non-hereditary because polycopies were found in the FISH method. No abnormality in tumor cells could be found in another unilateral case or in systemic cells of two bilateral cases.

CONCLUSION: A combination of FISH and RFLP methods can be used to diagnose some cases of RB as non-hereditary.

Pharmacokinetics of systemic versus focal Carboplatin chemotherapy in the rabbit eye: possible implication in the treatment of retinoblastoma

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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 microL), or a single application of carboplatin delivered by Coulomb-controlled iontophoresis (CCI; 14 mg/mL carboplatin, 5.0 mA/cm², 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.