Real-Time Ophthalmoscopic Findings of Superselective Intraophthalmic Artery Chemotherapy in a Nonhuman Primate Model

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Objective: To report real-time ophthalmoscopic findings during superselective intraophthalmic artery chemotherapy (SSIOAC) in a nonhuman primate model.

Methods: Six adult male Rhesus macaques (Macaca mulatta) were randomly assigned to 1 of 2 treatment cohorts: melphalan (5 mg/30 mL) or carboplatin (30 mg/30 mL). Each animal underwent 3 separate SSIOAC procedures at 3-week intervals. Digital retinal images were obtained during each infusion. Intravenous fluorescein angiography was performed immediately after each procedure.

Results: All SSIOAC procedures were successfully completed. Toxicities were equally distributed between drug cohorts. Systemic toxicities included mild bone marrow suppression in all animals and anorexia in 1. One animal had greater than 50% narrowing of the treated ophthalmic artery after its second infusion. All 18 procedures (100%) resulted in pulsatile optic nerve and choroid blanching, retinal artery narrowing, and retinal edema. Of the 18 procedures, retinal artery sheathing was found during 17 (94%), and retinal artery precipitates were seen in 10 (56%); choroidal hypoperfusion was seen by fluorescein angiogram in 18 (100%).

Conclusion: Real-time ophthalmic investigations are useful and, in our nonhuman primate model, indicate prevalent, acute ocular vascular toxicities during SSIOAC.

Clinical Relevance: Real-time retinal imaging is feasible in a nonhuman primate model of SSIOAC. Application to SSIOAC in children may shed insight into reported vascular toxicities.


W ith primary systemic chemotherapy moving to the forefront in the treatment of childhood retinoblastoma, progress has been made in saving eyes and vision.1-3 Yet, eyes are still lost to extensive disease, and children must endure the associated toxicities of systemic chemotherapy. In 2008, superselective intraophthalmic artery chemotherapy (SSIOAC) was put forth as a means of delivering high intraocular concentrations of chemotherapy to treat extensive disease while minimizing systemic exposure and its resultant toxicities.4 In those and further studies, there were no reports of adverse central nervous system events, limb loss, or bleeding diathesis.4,7 Reported adverse effects included transient pancytopenia, eyelid erythema and edema, and eyelash loss.4,8 Vision-threatening adverse effects have included ophthalmic artery (OA) thrombosis, retinal detachment, and nonclearing vitreous hemorrhage.4-13 More recently, delayed choroidal filling has been observed on intravenous fluorescein angiography after SSIOAC.14

Known mutagenic effects and concentration-dependent toxicities of melphalan (the current chemotherapeutic of choice) are cause for concern.15 To our knowledge, no data regarding ocular drug levels in SSIOAC have been published. Published clinical studies are only now reporting short-term and long-term ocular toxicity.4,14 Such limitations have led us to study SSIOAC in a nonhuman primate (NHP) preclinical model. The specific aims of our study were (1) to use real-time ophthalmic imaging to document the acute ocular toxicities during SSIOAC, (2) to measure the vitreous and systemic pharmacokinetics of chemotherapy administered via SSIOAC, (3) to describe the histopathologic features of NHP eyes treated by SSIOAC, and (4) to validate our NHP model by comparing orbital vascular anatomy with that of a 2-year-old child. We will address aims 2, 3, and 4 in sub-

See also pages 1399, 1407, 1487, 1490, and 1492
sequent reports. In this, our initial report, we address our first aim and describe real-time observations of SSIOAC in an NHP model and document acute retinal and choroidal vascular toxicities.

METHODS

Approval for the study was obtained from the Institutional Animal Care and Use Committee at the University of Tennessee Health Science Center, Memphis. All animals were maintained in a facility accredited by the Association for Assessment and Accreditation of Laboratory Animal Care and treated in accordance with the Guide for the Care and Use of Laboratory Animals and guidelines set forth by the Association for Research in Vision and Ophthalmology.

Six adult male Rhesus macaques (Macaca mulatta) were randomly assigned to 1 of 2 treatment cohorts: melphalan (5 mg/30 mL) or carboplatin (30 mg/30 mL). Each animal underwent 3 separate SSIOAC procedures spaced at 3-week intervals, with the right being the treated eye unless prohibited by vascular anomalies. Before each procedure, a baseline ophthalmic examination inclusive of indirect ophthalmoscopy with sclera depression was performed; digital retinal images were obtained using a RETCAM (Clarity Medical Systems, Pleasanton, California). The final procedure was terminal.

Under general anesthesia and using a sterile technique, percutaneous vascular access was gained through the right femoral artery using a 21-gauge butterfly needle with the animal in a supine position. A 0.018-in access guidewire was passed through the needle and the needle was removed. A 4F microaccess catheter was placed over its matched dilator, and the dilator and wire were removed. This was positioned in the descending aorta and used as a guide catheter for the microcatheter. The microaccess catheter was attached to a heparinized saline flush at a minimal flow rate to maintain patency using a rotating hemostatic valve. A Marathon 1.3F microcatheter was placed over a Mirage 0.08-in microguidewire (both from ev3 Neurovascular, Irvine, California) and the pair was used to selectively catheterize the right common carotid artery using uniplanar fluoroscopy, imaging in the frontal projection (OEC Series 9600; General Electric Health Care, Waukesha, Wisconsin). The animal’s head was then

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**Table. Data Collected for Each Animal**

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<th>Animal Identifier</th>
<th>Age, y</th>
<th>Weight, kg</th>
<th>Infusion No.</th>
<th>Blood Count</th>
<th>Fluoroscopy Time, s &lt;sup&gt;b&lt;/sup&gt;</th>
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<td>Initial</td>
<td>Final</td>
<td>Absolute Neutrophil Count</td>
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<td>Hemoglobin, g/dL</td>
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<td>2 NA NA NA 605</td>
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Abbreviations: CBP, carboplatin cohort; L, below normal (indicating mild bone marrow suppression); MEL, melphalan cohort; NA, not available.

To convert to SI factors: To convert hematocrit to a proportion of 1, multiply by 0.01; to convert hemoglobin to grams per liter, multiply by 10.0; to convert neutrophils to a proportion of 1.0, multiply by 0.56.

<sup>a</sup>Blood counts not measured after third infusion because third infusion was terminal.

<sup>b</sup>Per infusion.

<sup>c</sup>Animal was caught as an adult in 1989; thus, actual age unknown.

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**Figure 1.** Selective ophthalmic arteriograms from 1 primate in the carboplatin cohort (identified as 404) showing (A) successful initial catheterization with patient artery (A) and subsequent narrowing of artery during third infusion (B).
rotated onto its left side for a lateral projection. The right OA was superselectively catheterized using the microcatheter with minimal microguidewire manipulation. Nitroglycerine (100 µg/mL) was used as needed to limit flow-restricting vasospasm. A selective ophthalmic arteriogram using Optiray 320 (Mallinckrodt, Inc, St Louis, Missouri) was obtained to document position, anatomy, and antegrade flow. The designated chemotherapeutic was then infused for 30 minutes by pulsatile manual delivery (1 mL/min). Positioning of the microcatheter was checked fluoroscopically during infusion and after infusion. The catheter and access sheath were removed, and homeostasis was obtained using manual pressure.

Upon confirmed access of the OA, each drug was prepared, the solution pH was measured, and infusion was performed. Freeze-dried melphalan (50 mg; Bionchepharma, Lake Forest, Illinois) was reconstituted per the manufacturer's instructions with 10 mL of sterile diluents (provided by the manufacturer) to yield a 5 mg/mL concentration, 1 mL of which was subsequently diluted in 29 mL of normal saline to provide the desired 5 mg/30 mL concentration (5.5 pH). Three milliliters of 10 mg/mL carboplatin solution (APP, Schaumburg, Illinois) were diluted in 27 mL of normal saline to yield a 30 mg/30 mL concentration (5.0 pH). A 5-mL infusion of vehicle (normal saline, 5.5 pH) was performed immediately before drug delivery to serve as internal control following our first 2 procedures.

Immediately before infusion of the chemotherapeutic, a 1200 pediatric RETCAM lens was placed on the cornea of the right eye, and the optic, macula, and vascular arcades were imaged to assure flow through the central retinal artery. The lens was left in place throughout the study, and serial images were obtained. Upon completion of the infusion, intravenous fluorescein angiography was performed using 1 mL of 10% fluorescein dye.

Animals were followed up daily after SSIOAC treatments by veterinarians. Activity, diet, and blood counts were monitored. Weekly ophthalmic examinations were performed under intramuscular ketamine hydrochloride sedation. Digital external and retinal images were obtained.

A 1200 EX transmission electron microscope (JOEL USA, Peabody, Massachusetts) was used to examine the chemotherapeutic solutions with a CCD XR 11 camera (Advanced Microscopy Techniques, Woburn, Massachusetts). Solution samples were prepared in the same manner as for infusion and used as internal controls.
within 1 hour of preparation. A 10-µL aliquot of each solution was placed on 300-mesh carbon-coated grids and dried under a hood for 15 minutes. Any excess solution thereafter was wicked away, and the grids were allowed to dry.

RESULTS

The pretreatment characteristics of the NHPs are listed in the Table. Each animal was successfully treated with 3 cycles of SSIOAC. The right OA was accessed less than 2 mm distal to its ostium. For 10 of the 18 procedures, 1 mL of 100 µg/mL of nitroglycerine was used to minimize potential vasospasm. During the final procedure in 1 primate in the carboplatin cohort (identified as 404), narrowing of the OA proximal to the origin of the central retinal artery was observed, necessitating 2 separate injections of nitroglycerine (Figure 1). Because antegrade flow was present, albeit slowed, we continued with the procedure. The optic nerve maintained normal perfusion through the central retinal artery. No other complications related to arterial access or microcatheter placements were observed.

The only noted behavioral change was loss of appetite in 1 primate, which persisted for approximately 1 week after each procedure. The median weight of the animals (11.6 kg) did not change throughout the study. After the first 2 treatments, all animals had mild bone marrow suppression, with hematocrits, hemoglobins, and absolute neutrophil counts dipping just below normal range for the species (Table).

Baseline ophthalmic examinations were remarkable only for a corneal scar from a prior ulcer in the right eye of 1 primate in the melphalan cohort (identified as 561). The toxicities documented by real-time ophthalmic imaging in nearly all perfusions are shown in Figure 2. During each infusion, there was visible pulsatile pallor of the optic nerve (Figure 3 and Figure 4) coincidental with drug delivery. Four of the 18 procedures (22%) had simultaneous choroidal blanching. The choroid and optic nerve re-perfused between each pulsation. Pretreatment vehicle infusion resulted only in pulsatile changes in the optic nerve. As the infusion progressed, we observed narrowing of the retinal artery with associated sheathing in some cases (as seen in intravenous fluorescein angiography; Figures 5, 6, and 7). The inferior temporal and nasal arcades were most often affected.

Precipitates spontaneously appeared in the retinal arteries in 56% (10 of 18; 5 in each cohort) of the procedures, sometimes filling the arterial tree. The extent and duration of the precipitates varied, appearing from 7 to 20 minutes into an infusion. In each instance, there had been antecedent marked narrowing of the retinal arteries with or without associated sheathing of the vessels. What were believed to be coinciding choroidal infarcts were simultaneously seen. Most precipitates cleared over minutes, completely resolving by the end of each infusion.

Figure 4. Real-time retinal observations during carboplatin infusion: A, pulsatile optic nerve pallor with retinal edema and narrowing of the retinal arteries, B, re-perfusion of the optic nerve between pulsations, C, retinal artery precipitates, and D, clearing of the precipitates with underlying choroidal abnormalities.
Using intravenous fluorescein angiography, we saw delayed choroidal filling and persistent areas of nonperfusion following each study (Figures 5-7). The observed choroidal changes differed in severity among the procedures and animals, with delays in choroid filling lasting from seconds to minutes. Persistent choroidal nonperfusion was sec-

![Figure 5. Intravenous fluoroscopic angiography for each infusion in all 6 animals.](image)

![Figure 6. Intravenous fluoroscopic angiography corresponding to Figure 3: A, delayed, sectoral choroidal filling; B, persistent areas of choroidal nonperfusion with early artery sheathing and diffuse capillary dropout; C, persistent sheathing of the arteries, early optic hyperfluorescence, and leakage from parafoveal vessels; and D, late frame showing progressive sheathing, leakage, optic nerve hyperfluorescence, and hypoperfusion of the nasal choroid and retina.](image)
toral in nature. In some cases, truncation of the retinal arterial tree and diffuse retinal capillary drop-out coincided with delayed filling of the retinal veins.

Interval dilated fundus examinations (Figure 8) showed resolution of acute vasculopathies. However, nerve fiber layer infarcts and intraretinal hemorrhages persisted in most animals between procedures (Figure 9). No persistent optic nerve pallor or orbital toxicities were observed. Persistent right upper eyelid edema and anisocoria (larger treated pupil; no relative difference in pupils between light and dark) were noted in 2 animals each. A definitive afferent pupillary defect was not documented in either animal.

Both chemotherapeutic solutions contained particles when examined by transmission electron microscopy. The melphalan solution had particulate aggregates approximately 5 µm in size. Crystals (2 µm) were found in the carboplatin solution (Figure 10).

COMMENT

We successfully completed 18 SSIOAC procedures in 6 NHPs (3 per animal). Our NHPs tolerated the procedure with minimal observed systemic toxicities—mild bone marrow suppression in all and anorexia in 1. In contrast, ophthalmic vascular toxicities were significant and equally distributed between both cohorts (Figures 2, 5, and 8). Recent studies report similar vasculopathies remote to SSIOAC, including sectoral choroidal occlusive vasculopathy, retinal arteriolar emboli, central and branch retinal artery occlusion, transient vasospasm with visual loss, diffuse exudative angiopathy, and vitreous hemorrhage.9-14 Our real-time study suggests the acute ocular vascular toxicities occurring during treatment are significantly greater.
than those observed at weeks 1, 2, and 3 after the procedure.

However, we can monitor the ocular vasculopathy only during SSIOAC; the resultant damage to the OA and its branches cannot be discovered until subsequent selective angiograms, as we and others have shown10 (Figure 1). An OA thrombosis was noted in 1 animal on selective OA angiogram during the final procedure. More than 50% narrowing of the right OA proximal to the origin of the central retinal artery was observed. Interval dilated examinations of the right eye after the second SSIOAC had shown only nerve fiber infarcts and intraretinal hemorrhages. The central artery was perfused, and the optic nerve appeared normal.

We believe that our observed vascular toxicities and those reported in children are best explained by previously reported in vitro studies17 on cultured human retinal vascular endothelial cells, in which a 1-hour exposure to a 4-µg/mL melphalan dose increased cell death by greater than 6-fold. Surviving cells showed a significant increase in migration and proliferation. Upregulation of inflammatory mediators ICAM-1 (intercellular adhesion molecule 1) and interleukin 8—both promoters of leukostasis similar to that found in diabetic retinopathy—was seen.18 Thus, the concentrations of melphalan being used for SSIOAC may induce vaso-occlusive disease,15 which may lead to observed sight-threatening vasculopathies. These vasculopathies may be compounded by the concurrent disruption of blood flow with pulsatile delivery and presence of particulates, as we observed. A review of the literature19 indicates that disruption of blood flow promotes vascular endothelial cell inflammation and apoptosis.

The effect of the infused solutions’ pH must also be taken into consideration.20 Most intravenous solutions have an acidic pH, due in part to the delivery vehicle, yet are generally well tolerated. Melphalan and carboplatin (pH 5.5 and 5.0, respectively) are typically infused into large-caliber venous vessels, minimizing the effect of pH. The effect of an acidic solution on a small-caliber artery is not known but should raise concerns similar to those previously voiced regarding acid-induced thrombophlebitis.21,22 During infusion of our control vehicle (normal saline [pH of 5.5]), no toxicities were observed. To our

Figure 9. Posttreatment examination of animal in Figures 4 and 7 showing resolution of parfoveal arteriole occlusions with watershed infarcts and resultant retinal atrophy after 1 week (A), 2 weeks (B), and 3 weeks (C).

Figure 10. Transmission electron microscopy of melphalan solution (5 mg/30 mL) showing 5-µm particle aggregates (A) and carboplatin solution (30 mg/30 mL) showing 2-µm crystals (B).
knowledge, no current clinical SSIOAC study has commented on or made reference to solution pH. We believe pH may play an important role in the observed vascular toxicities. The need for pH adjustment and subsequent effect on drug solubility should be addressed.

We must also comment on the retinal arterial precipitates seen in 6 of our animals during 10 different infusions. Each solution, when examined by transmission electron microscopy, showed particles—5-µm aggregates in the melphanal and 2-µm crystals in the carboplatin (Figure 10). We do not believe these particles solely account for the retinal artery precipitates. We hypothesize that our findings resulted from a complex interaction among inflammatory mediators, leukostasis, and the particulates seen on electron microscopy, which could be in keeping with reported retinal arteriole emboli or Roth spots. Clearly, further investigation is needed.

Last, we must address the relevance of our preclinical model. Prior studies32-23 have shown Rhesus macaques are a valid model to study anticancer drug pharmacokinetics because they are large enough for repeated sampling, inclusive of blood and cerebrospinal fluid. Furthermore, the size and weight of an adult male Rhesus macaque is comparable with that of a human 2-year-old, the age of a child most likely to undergo SSIOAC. These similarities provided us a means to better understand the SSIOAC, most notably the acute vascular occlusions. We encourage those who have to investigate the SSIOAC, most notably the acute vascular occlusion, for SSIOAC, and the age of a child most likely to undergo SSIOAC. Furthermore, the size and weight of an adult male Rhesus macaque is comparable with that of a human 2-year-old, the age of a child most likely to undergo SSIOAC. These similarities provided us a means to better understand the SSIOAC, most notably the acute vascular occlusions. We encourage those who have to investigate the SSIOAC, most notably the acute vascular occlusion, for SSIOAC, and the age of a child most likely to undergo SSIOAC. Furthermore, the size and weight of an adult male Rhesus macaque is comparable with that of a human 2-year-old, the age of a child most likely to undergo SSIOAC.

As an institution, we have not yet adopted SSIOAC for the treatment of intraocular retinoblastoma in our patients. We encourage those who have to investigate the questions we have raised, specifically with regard to acute vascular toxicities, drug concentration, pH, and particulates. In turn, we will pursue our questions in preclinical models. In conclusion, we believe we have shown there is considerable merit in documenting real-time observations during SSIOAC.

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