

Bilateral Superselective Ophthalmic Artery Chemotherapy for Bilateral Retinoblastoma: Tandem Therapy

We previously described our initial experience with superselective ophthalmic artery delivery of chemotherapy for advanced retinoblastoma and emphasized that it was both effective and safe for both the patient and eye.\(^1\)\(^2\) In each of those cases, only 1 eye was treated with this novel technique. We now report on the first 4 patients with advanced (Reese-Ellsworth group V) bilateral disease in whom initial management was bilateral treatment accomplished during the same treatment session.

Report of Cases. Four children with bilateral Reese-Ellsworth group V retinoblastomas (4 with bilateral Vb, 1 with Vb in one eye and Va in the fellow eye; international classification, C:4, D:1, and E:3) were initially treated with a superselective arterial infusion (ophthalmic artery) of chemotherapy and were followed up every 3 to 4 weeks with examinations while under anesthesia. The chemotherapy was delivered to both eyes in the same session by first passing a catheter into 1 ophthalmic artery and infusing chemotherapy, retracting the catheter back to the aorta, and then extending it into the fellow carotid artery and up into the fellow ophthalmic artery (tandem therapy). Focal therapy with laser hyperthermia (transpupillary thermotherapy) to small tumors and cryotherapy to intermediate tumors was subsequently performed (Figure).

There were 2 boys and 2 girls in the study group; their ages at treatment were 6 months, 5 months, 15 months, and 19 months. One child had a family history of retinoblastoma and all had bilateral disease at initial diagnosis. The macula was involved with the tumor in all cases. Pretreatment electroretinography (ERG) was performed on 6 of the 8 eyes; flicker potentials were 22.1 µV, 22.4 µV, 33.4 µV, 71.7 µV, and 105.5 µV, and “barely detectable” in 1 case. Follow-up ranged from 8 to 17 months (mean, 12.75 months), and 2 of the patients were followed up for more than 1 year. Melphalan was used alone in 2 patients and melphalan plus topotecan was used in 2 patients. Sessions were performed at 3- to 4-week intervals, and the total number of sessions ranged from 1 to 3 (mean, 2.3). One patient had only 1 session. No patient received external beam radiation or plaque therapy. The total doses of melphalan per tandem session (adding the dose from the right and left eyes) was 4 mg in 1 session, 5 mg in 8 sessions, and 5.5 mg in 1 session; for topotecan, doses were 0.3 mg in 3 sessions, 0.5 mg in 1 session, and 1 mg in 1 session. Topotecan was added for the eyes with more advanced disease.

All patients are alive and free of metastatic disease. No eye needed to undergo radiation or enucleation after intraarterial chemosurgery. There have been no intraoperative or postoperative vascular complications. No patient has received a port or transfusion of any type, required hospitalization, or developed fever/neutropenia. There have been no grade 4 events. One patient developed grade 3 neutropenia with each of 3 infusions of melphalan (total doses: 5, 5, and 4 mg).

All tumors and the vitreous seeds in each case showed significant reduction in size within 3 weeks of treatment. The most recent ERG results were classified as poor (0.2–25.0 µV), fair (25.1–50.0 µV), good (50.1–75.0 µV), and excellent (>75.0 µV). Of the 6 eyes having evaluable ERGs before treatment, the ERG results were poor in 1, fair in 3, good in 1, and excellent in 1. After all treatments, the ERG results improved in 3 eyes, stayed the same in 1 eye, and diminished in 2 eyes. Posttreatment ERGs were available for 8 eyes and were poor in 3, good in 1, and excellent in 4.

Pretreatment and final posttreatment RetCam (Clarity Medical Systems Inc, Pleasanton, California) photographs of each of the eyes are presented in the Figure. Some eyes had transpupillary thermotherapy laser or cryotherapy (for small tumors in the eye).

Comment. The concept of intraarterial chemotherapy for retinoblastoma was introduced by Reese et al\(^1\) more than 50 years ago. The alkylating agent triethylene melamine was used via puncture sites in the carotid artery on the side of the eye to be treated. Reese et al reported good results in hundreds of eyes but other investigators (lead by A. Kaneko, MD)\(^4\)\(^5\) introduced selective chemotherapy for retinoblastoma. These investigators developed a catheter that is passed from the groin (femoral artery) into the carotid artery on the side to be treated. A balloon in the catheter is then inflated, occluding the carotid, and chemotherapy is infused proximal to the occlusion. Our technique involves superselective infusion directly into the ophthalmic artery. Unlike systemic chemotherapy for retinoblastoma, the technique has fewer systemic adverse effects; requires no port, hospitalizations, or transfusions; and may be curative alone. This study highlights the fact that now both eyes of the same patient can be treated with this technique during the same session of anesthesia, and despite the “double dose” of chemotherapy, there were no significant systemic adverse effects. The eyes experienced no significant adverse effects either and the ERG results actually improved in half of the eyes for which measurements were avail-

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able before treatment. In 2 cases, the ERG results diminished after treatment (from fair to poor in one case and fair to flat in another). This child's ERG results did not diminish when only melphalan was used; when topotecan was added in the last session, the ERG results in both eyes decreased. We have subsequently changed the dose of topotecan and continue to use this agent without problems.

Bilateral intraarterial chemotherapy for bilateral retinoblastoma (tandem therapy), even when advanced (Reese-Ellsworth group V), appears to be safe for the patient and eye and can avoid the use of multiagent systemic chemotherapy, enucleation, and/or radiation in any form for children with bilateral Reese-Ellsworth V eyes. Our protocol for treatment began in May 2006, but longer follow-up is needed to see if any future complications will develop.

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2. Brodie SE, Pierre Gobin Y, Dunkel IJ, Kim JW, Abramson DH. Persistence of retinal function af-

Figure. Pretreatment and corresponding posttreatment fundus appearance. Transpupillary thermotherapy (TTT) laser and cryotherapy applications are listed for each eye.
Evisceration in Unsuspected Intraocular Tumors

Enucleation and evisceration are the 2 possible surgical management options for a disfigured or a painful blind eye.1-3 Evisceration is replacing enucleation as the favored surgical option because of its potential advantages such as superior cosmesis, better prostheses motility, and fewer implant-related complications.1-3 Evisceration, however, is absolutely contraindicated in suspected intraocular malignancy. Before the availability of modern imaging techniques, 10% of blind, painful eyes with opaque media were found to contain unsuspected malignant tumors on histopathologic examination.1,4 Although rare, pathologists continue to encounter clinically unsuspected intraocular tumors during histopathologic examination of eviscerated eyes. Several anecdotal studies of unsuspected tumors found after evisceration exist.4-13 Although these articles include cases of carcinoma of the nonpigmented ciliary epithelium, adenoscarcoma of the retinal pigment epithelium, choroidal lymphoma, choroidal ganglion cell tumor, spindle cell neoplasm, and retinoblastoma, uveal melanoma predominates. Eagle et al13 recently described a series of 7 additional cases of unsuspected uveal melanoma diagnosed in eviscerated specimens and have emphasized the role of detailed a medical history, clinical evaluation, and appropriate imaging before performing evisceration in painful blind eyes with opaque media. Our series comprises 6 cases of unsuspected intraocular tumors diagnosed following evisceration and elaborates on the lessons learned from this experience.

Methods. This is a retrospective, non-randomized, clinicopathological case series of patients with previously unsuspected intraocular tumors diagnosed by histopathology of eviscerated blind eyes. The cases were collected by searching the indexed ocular pathology registry from January 1998 to December 2007 at a tertiary care center in southern India. The medical records were reviewed for patient age, sex, symptoms, initial clinical findings, initial clinical diagnosis, imaging, prior treatment, indication for evisceration, intraoperative findings, histopathology, postenucleation management, and final outcome for local tumor recurrence and systemic metastasis.

Results. We identified 6 patients with unsuspected intraocular tumors who had undergone evisceration (Table). The median patient age was 18 years (range, 8-70 years; mean [SD], 27.17[22.46] years), and 5 were male. Preoperative ultrasound B-scan was available for 3 patients; a review of the documented images showed no obvious intraocular mass in 2 patients. A preoperative computed tomographic scan in one patient did not reveal a retrobulbar mass. Indications for evisceration included a painful blind eye in 4 patients, cosmetic concern in 1 patient, and a perforated hypotonic eye with uveal prolapse in 1 patient. No surgeons had recorded unusual features of intraocular contents observed during evisceration. Eviscerated tissue was not submitted for histopathology in 2 patients. Histopathology of the eviscerated tissue or biopsy from the recurrent orbital tumor revealed retinoblastoma in 2 patients, and 1 each of uveal melanoma, adenoscarcoma of the ciliary body, choroidal ganglion cell tumor, conjunctival squamous cell carcinoma with intraocular invasion. Orbital exenteration was eventually required to treat 4 of these patients. Two patients with retinoblastoma were treated with high-dose chemotherapy, orbital exenteration, and external beam radiotherapy. The patient with uveal melanoma had orbital exenteration and external beam radiotherapy. Adenocarcinoma of the ciliary body was managed with enucleation and external beam radiotherapy. The patient with benign choroidal ganglion cell tumor was observed. The patient with intraocular invasion of conjunctival squamous cell carcinoma had orbital exenteration. All of the patients were free of local recurrence or systemic metastasis at a median follow-up of 28 months (range, 4-41 months; mean [SD], 24.50[14.90] months).

Report of Cases. Case 1. A systemically healthy and active 3-year-old boy presented to the glaucoma clinic in June 2001 with spontaneous progressive enlargement of the left eye of 2 years’ duration. There was no history of prior trauma or surgery. Findings of the examination of right eye were essentially normal. The child had no light perception in the left eye. There was ciliary staphyloma, diffuse corneal edema, dilated fixed pupil, aphakia, and an intraocular pressure of 34 mm Hg by Perkin applanation tonometry under anesthesia. The fundus view was unclear. Ultrasound B-scan showed an increase in the axial length, a clear vitreous cavity, and optic disc cupping (Figure 1A). There was no evidence of subluxation of the crystalline lens or an intraocular mass. An immersion ultrasound B-scan, however, was not done. The glaucoma specialist performed semiconductor diode laser transscleral cyclophotocoagulation to control the intraocular pressure. The child had periodic follow-up at the glaucoma clinic thereafter. The child reported severe pain in the left eye in January 2005 and had evisceration by a pediatric ophthalmologist. A repeated ultrasound B-scan of the eye was not performed before evisceration. Histopathology of the eviscerated tissue showed a malignant round cell tumor with areas of necrosis and calcification, based on which a diagnosis of retinoblastoma was made (Figure 1B and C), and the child was referred to the ocular oncology service. A computed tomographic scan did not reveal optic nerve invasion or orbital extension (Figure 1D). There was no evidence of systemic metastasis. Results of bone marrow biopsy and cerebrospinal fluid cytology were negative.