Intra-arterial Chemotherapy for Retinoblastoma in 70 Eyes

Outcomes Based on the International Classification of Retinoblastoma

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Objective: To analyze our 5-year experience of intra-arterial chemotherapy (IAC) for retinoblastoma as primary or secondary therapy.

Design: Retrospective interventional case series.

Participants: A total of 70 eyes of 67 patients.

Intervention: Ophthalmic artery chemotherapy infusion under fluoroscopic guidance was performed using melphalan (3, 5, or 7.5 mg) in every case, with additional topotecan (1 mg) and/or carboplatin (30 or 50 mg) as necessary.

Main Outcome Measures: Tumor control and treatment complications.

Results: The mean patient age at IAC was 30 months. The treatment was primary in 36 eyes and secondary in 34 eyes. Those primary therapy eyes were classified according to the International Classification of Retinoblastoma (ICRB) as group A (n = 0), B (n = 1), C (n = 4), D (n = 17), or E (n = 14). The secondary therapy eyes had failed previous intravenous chemotherapy (n = 34) in every case. Each eye received a mean of 3 IAC sessions per eye (median, 3; range, 1−7 sessions). After IAC with a mean follow-up of 19 months, globe salvage was achieved in 72% of primary-treated cases and in 62% of secondary-treated cases. Specifically, primary therapy achieved globe salvage for group B (100%), group C (100%), group D (94%), and group E (36%). Of all 70 eyes, complete regression was achieved for solid tumor in 48 of 51 eyes (94%), subretinal seeds in 40 of 42 eyes (95%), and vitreous seeds in 34 of 39 eyes (87%). After each catheterization (n = 198), the main complications included transient eyelid edema (5%), blepharoptosis (5%), and forehead hyperemia (2%). More lasting complications included vitreous hemorrhage (2%), branch retinal artery obstruction (1%), ophthalmic artery spasm with reperfusion (2%), ophthalmic artery obstruction (2%), partial choroidal ischemia (2%), and optic neuropathy (<1%). Over the past 3 years, the combined incidence of ophthalmic, retinal, and choroidal vascular ischemia was reduced to 1%. There was no patient with stroke, seizure, neurologic impairment, limb ischemia, secondary leukemia, metastasis, or death.

Conclusions: Five-year experience with IAC indicates that this technique is remarkably effective for the management of retinoblastoma as both a primary and a secondary treatment. *Ophthalmology 2014;■:1−8 © 2014 by the American Academy of Ophthalmology.*

Intra-arterial chemotherapy (IAC) has assumed a major role in the management of retinoblastoma. This targeted therapy involves the delivery of potent chemotherapy directly into the ophthalmic artery of a child to effectively treat a retinoblastoma within the eye and minimize systemic absorption. The history of this technique has been reviewed in previous publications.[1−7] The method of chemotherapy delivery has evolved over time from the initial Japanese technique of catheterization with balloon obstruction to the American technique of selective ophthalmic artery catheterization for the delivery of chemotherapeutic agents directly into the vascular tree that serves the eye and tumor.[1−7]

Previous publications have heralded the success and complications of IAC for retinoblastoma.[3−16] Success is mostly dependent on the degree of vitreous and subretinal tumor seeding, as well as tumor size. Treatment complications can manifest as a mechanical effect, such as periocular edema and erythema. Likewise, chemotherapy infusion can lead to toxic effects on the vascular endothelium.[10,12−14] We report our 5-year experience with IAC for retinoblastoma with a focus on treatment results based on primary or secondary therapy and on the International Classification of Retinoblastoma (ICRB)[17] to allow the clinician an estimate of the potential outcome with this approach.

Methods

The study subjects included patients with unilateral or bilateral intraocular retinoblastoma undergoing IAC from January 2009 to

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Table 1. Intra-arterial Chemotherapy for Retinoblastoma as Primary or Secondary Management in 70 Eyes: Demographics

Features at Time of IAC	No. (%)
Mean age (mos) (n = 67 patients)	
(median, range)	30 (20, 4–392)
Ethnicity (n = 67 patients)	
Caucasian	38 (57)
African American	13 (19)
Hispanic	6 (9)
Asian	6 (9)
African	1 (2)
Arab	3 (4)
Sex (n = 67 patients)	
Female	41 (61)
Male	26 (39)
Heredity (n = 67 patients)	
Sporadic	59 (88)
Familial	8 (12)
Genetics (n = 62 patients)	
Somatic	34 (55)
Germline	28 (45)
Laterality* (n = 67 patients)	
Unilateral	42 (63)
Bilateral	25 (37)
Eyes undergoing treatment (n = 70 eyes)	
Right	33 (47)
Left	37 (53)
Signs† (n = 70 eyes)	
Leukocoria	53 (76)
Strabismus	11 (16)
Anterior chamber seeds	1 (2)
Hyphema	1 (2)
Iris neovascularization	9 (13)
Ectropion uveae	1 (2)
Vitreous hemorrhage	3 (4)

IAC = intra-arterial chemotherapy.
*Both eyes were treated with IAC in 3 patients.
†Total percentage adds up to >100% because some patients had >1 sign.

June 2013. Exclusion criteria were patient age <4 months, vitreous hemorrhage, secondary glaucoma, and extension of tumor into the optic nerve, uvea, anterior segment, or extrascleral compartments. Other exclusionary details were patients with a history of blood dyscrasia or thrombotic events. Informed consent was obtained from the parent or guardian, and the associated risks of ocular, neurologic, and systemic toxicity were explained in detail. Institutional review board approval was obtained for this retrospective study.

The patients were examined under anesthesia by the treating ocular oncologist. Meticulous examination was conducted with indirect ophthalmoscopy, and details were documented with large fundus drawings. Photographic documentation of each affected eye was performed by external photography, wide-angle fundus photography, fluorescein angiography, and B-scan ultrasonography. The decision to treat with IAC was undertaken in consultation with an ocular oncology team (C.L.S., S.E.L., J.A.S.), endovascular neurosurgeon (P.J.), and pediatric oncologist (E.H.C.) at Wills Eye Hospital of Thomas Jefferson University, Philadelphia, Pennsylvania.

Our technique of the IAC procedure has been described elsewhere.[1,3,6] The procedure is performed under general anesthesia using a sterile technique. Anticoagulation with intravenous infusion of heparin (50 IU/kg) is delivered to a target activating clotting time of 2 to 3 times baseline. Through a transfemoral approach, the ipsilateral internal carotid artery is catheterized with a 4F pediatric guide catheter. The arterial anatomy is visualized with serial angiography runs, and the ostium of the ophthalmic artery is superselectively catheterized with a Prowler 10 microcatheter (Codman & Shurtleff, Inc., Raynham, MA). A superselective injection through the microcatheter is performed to check adequate positioning and assess the amount of reflux, if any, into the internal carotid artery before chemotherapy is injected. Eyes with vascular anomalies that failed ophthalmic artery catheterization were treated with catheterization and balloon obstruction.[2] Chemotherapeutic medications included melphalan, topotecan, or carboplatin. The melphalan dose was 3, 5, or 7.5 mg, increasing with patient age and tumor size. Topotecan dose was 1 mg, and carboplatin dose was 15 or 30 mg. All patients received melphalan, and those with more extensive disease, particularly with vitreous seeding,

Table 2. Intra-arterial Chemotherapy for Retinoblastoma as Primary Therapy According to the International Classification of Retinoblastoma in 36 Cases

	Findings at Initial Presentation					Tumor Control with IAC at Final Follow-up				
ICRB Group (n = 36 Eyes)	*Mean Tumor Diameter (mm)*	*Subretinal Seeds*	*Vitreous Seeds*	*Subretinal Fluid*	*IAC Medications (n)*	*Tumor*	*Subretinal Seeds*	*Vitreous Seeds*	*Subretinal Fluid*	*Globe Salvage*
A (n = 0)	na	na	na	na	na	na	na	na	na	na
B (n = 1)	8	0	0	1	M (1)	1 (100%)	na	na	1 (100%)	1 (100%)
C (n = 4)	13	4	0	4	M (4)	4 (100%)	4 (100%)	na	4 (100%)	4 (100%)
D (n = 17)	19	11	11	12	M (9) M+T (5) M+C (3)	17 (100%)	11 (100%)	10 (91%)	10 (83%)	16 (94%)
E (n = 14)	21	9	10	9	M (11) M+T (2) M+C (1)	12 (86%)	9 (100%)	8 (80%)	6 (67%)	5 (36%)
Total (n = 36)	20	24	21	26	M (25) M+T (7) M+C (4)	34 (94%)	24 (100%)	18 (86%)	21 (81%)	26 (72%)

C = carboplatin; IAC = intra-arterial chemotherapy; ICRB = International Classification of Retinoblastoma; M = melphalan; na = not available; T = topotecan.