ONLINE FIRST

Intra-arterial Chemotherapy for Retinoblastoma

Report No. 1, Control of Retinal Tumors, Subretinal Seeds, and Vitreous Seeds

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Objective: To describe tumor control following intra-arterial chemotherapy (IAC) for retinoblastoma.

Methods: A retrospective interventional series in which 17 patients were treated with ophthalmic artery injection of melphalan, 5 mg, was undertaken to determine retinoblastoma control.

Results: Of 190 children with retinoblastoma, 17 (9%) were treated with IAC. Catheterization was successful in 37 of 38 attempts. The treatment was primary in 13 cases (1 failed catheterization) and secondary in 4. The median retinoblastoma base was 20 mm and the median retinoblastoma thickness was 9.0 mm. Iris neovascularization was present in 5 cases. Following IAC, complete response of the main tumor was found in 14 cases (88%) and partial response was found in 2 (12%). Eyes with complete response and followed up for a minimum of 1 year (n=10) showed no solid tumor recurrence. Of 11 eyes with subretinal seeds, 9 (82%) had complete response, 1 (9%) had partial response, and 1 (9%) had recurrence. Of 9 eyes with vitreous seeds, 6 (67%) had complete response, 2 (22%) had partial response, and 1 (11%) had recurrence. Globe salvage was achieved in 8 of 12 eyes (67%) treated with primary IAC, including 2 of 2 group C eyes, 4 of 4 group D eyes, and 2 of 6 group E eyes according to the International Classification of Retinoblastoma. Globe salvage was achieved in 2 of 4 eyes (50%) treated secondarily after failure of other methods.

Conclusions: Of 12 eyes managed with IAC as primary treatment, globe salvage was achieved in 67%. Eyes classified as group C or D showed 100% globe salvage, whereas group E had 33% salvage. Of 4 eyes managed with IAC as secondary treatment, globe salvage was achieved in 50%.

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FOR MORE THAN 40 YEARS, WE have followed contemporary approaches in the management of retinoblastoma with options of enucleation, chemotherapy, and established methods of laser photocoagulation, thermotherapy, cryotherapy, plaque radiotherapy, and external beam radiotherapy.[1-4] Most of these

See also pages 1407, 1458, 1487, 1490, and 1492

therapies were eventually realized to have limitations and specific indications. During the past 2 decades, we have come to understand the benefits, limitations, and risks of systemic intravenous chemoreduction for retinoblastoma.[5-7] Now, during the past 2 years, our team in Philadelphia, Pennsylvania, has cautiously evaluated intra-arterial chemotherapy (IAC) for retinoblastoma.

Historically, chemotherapy delivery into an artery leading to the eye was first explored by Reese et al[8] in 1958, combining triethylene melamine and x-ray treatment for retinoblastoma therapy. Later, Kiribuchi[9] used retrograde infusion of anticancer drugs into the ophthalmic artery. More recently, Japanese collaborators found melphalan to be the most effective chemotherapy,[10] and they evaluated delivery of melphalan into the ophthalmic artery by occluding distal flow in the internal carotid artery using catheterization and balloon occlusion.[11,12] They described the safety and success of this technique, but tumor control and complications were not clearly evident in their preliminary reports.

The technique of direct ophthalmic artery catheterization was further refined by Gobin and Abramson[13] in the United States using precise direct cannulation into the proximal ophthalmic artery for chemotherapy delivery under fluoroscopic guidance. Shields et al[14] illustrated the diffi-

culty of this technique, emphasizing the U-turn entry of the guide wire into the small-bore ophthalmic artery. Using this technique of direct cannulation, Abramson et al[15,16] provided observations of remarkable tumor response, describing large retinoblastomas showing complete regression similar to that with systemic intravenous chemoreduction.[6] However, the possible benefits of IAC include reduced dose of chemotherapy into the ophthalmic artery, thus minimizing systemic dose and toxic effects to the remainder of the body.[11,15]

Retinoblastoma can occur in the eye as a solid tumor in the retina, as tumor seeds in the subretinal space, and as tumor seeds in the vitreous cavity. Intra-arterial chemotherapy presumably adequately reaches the retina via the vascular system to face intraretinal retinoblastoma, but its full effect on subretinal and vitreous seeds is not clearly known. Hence, in this article, we evaluate our results with IAC for retinoblastoma control of solid tumor in the retina, subretinal seeds, and vitreous seeds.

METHODS

Institutional review board permission was obtained for this retrospective study on September 15, 2008. Inclusion criteria were the presence of viable unilateral or bilateral retinoblastoma in patients aged 4 months or older in whom the only other options would be enucleation, external beam radiotherapy, or systemic chemoreduction. Patients were excluded if the retinoblastoma could be controlled with more conservative methods of cryotherapy, thermotherapy, or plaque radiotherapy. Parents and patients were informed of the risks of ophthalmic artery cannulation, including brain or orbital hemorrhage, infection, and inflammation, loss of visual acuity, loss of the eye, anaphylaxis, stroke, and death. Parents and patients were also informed of the unknown risks of systemic metastasis from retinoblastoma using this technique and long-term ocular and systemic toxic effects. Exclusion criteria included opaque or hazy media that precluded visualization of the fundus, fresh or recurrent retinoblastoma that could be amenable to other conservative therapies, and clinical evidence suggestive of retinoblastoma invasion into the optic nerve, choroid, sclera, orbit, or metastatic sites.

Each patient was examined initially in the office (C.L.S., G.C.G., and P.J.) and then under anesthesia (C.L.S.) with large fundus drawings, photographic documentation, and fluorescein angiographic analysis of all tumors and features in each eye. The decision for IAC was made in consultation with members of the Ocular Oncology Service at Wills Eye Institute (C.G.B., S.E.L., and J.A.S.), the Department of Neurosurgery and Interventional Neuroradiology (R.R. and P.J.), and the Department of Pediatric Oncology (G.C.G.), Thomas Jefferson University. Family history and medical history, particularly for thrombotic events, were obtained. This information was used to assess the need for screening tests looking for an increased risk of thrombosis, including factor V Leiden mutation, methylene tetrahydrofolate reductase mutation, and prothrombin 20-21-0 mutation.

After parent or legal guardian consent, the IAC catheterization procedure was performed in the operating room under general anesthesia as an outpatient procedure. Anticoagulation with intravenous heparin (75 IU/kg) was delivered. A 4-French arterial sheath was placed into the prepared and draped femoral artery region. The French (1.3-mm-diameter) catheter was guided into the ipsilateral internal carotid artery using fluoroscopic guidance. Serial arteriograms were taken to visualize the eye and cerebral vasculature and to select the best approach, showing the path of the ophthalmic artery from the internal carotid artery. Using fluoroscopy and roadmapping, the ipsilateral proximal portion of the ophthalmic artery was catheterized with a 450-μm microcatheter and a confirmatory angiogram was taken. Chemotherapy, diluted in 30 mL of saline, was delivered using a pulsatile, nonlaminated technique over 30 minutes to maximize homogeneous drug delivery. The selected chemotherapy drug was melphalan (5 mg) in all cases and additional carboplatin (30 mg) was used initially based on previously documented efficacy.[15] Carboplatin was later discontinued after observations of ophthalmic or retinal vascular attenuation, as platinum-based drugs are known to have a sclerosing effect.[17,18] After the infusion was completed, the catheters were withdrawn, the femoral sheath was removed, and hemostasis of the femoral artery by manual compression was achieved. The child was awakened and observed for 6 hours, then discharged the same day. A sterile dressing over the cannulation wound in the leg was maintained for 2 days, and the site was treated with topical antibiotic ointment. Oral aspirin (40 mg) was delivered for 2 weeks.

Following the initial IAC, each patient was evaluated by ocular oncology and pediatric oncology on a 3- to 4-week basis until tumor control was achieved. The ophthalmic examination was performed under general anesthesia with complete ocular evaluation including large retinal drawing, fundus photography with a Retcam camera (Massie Industries, Dublin, California), fluorescein angiography, and electroretinography. The pediatric examination included complete history and physical, height and weight, complete blood cell count, and blood chemistry; magnetic resonance imaging of the brain and orbit were performed twice yearly until age 5 years.

Each patient was scheduled to receive 3 session of IAC at monthly intervals. However, if complete regression was documented with no sign of tumor or seed viability, then further IAC was not performed. After stable follow-up, ophthalmic oncology and pediatric oncology examinations were repeated at 3 months, 4 months, and then every 6 months thereafter.

Each patient was evaluated for age at diagnosis (months), race (African American, Asian, Hispanic, white), sex (male, female), and hereditary pattern (sporadic, familial). Prior treatments were recorded. A comprehensive ocular examination under anesthesia was performed with assessment for laterality of involvement (unilateral, bilateral), International Classification of Retinoblastoma, Reese-Ellsworth classification of retinoblastoma, intraocular pressure (by Schiotz tonometry), and status of the eye. Detailed fundus drawings, Retcam fundus photography, ultrasonography, fluorescein angiography, and electroretinography were performed. Each tumor was analyzed for size in greatest basal dimension (millimeters) and thickness (millimeters) using indirect ophthalmoscopy and ultrasonography, distance to the optic nerve and foveola (millimeters), associated vitreous seeds (present, absent), extent of vitreous seeds, associated subretinal fluid (present, absent), percentage of retina detachment (0%-100%), and subretinal tumor seeds (present, absent) and their location.

At each examination under anesthesia, clinical features were recorded. The tumor response was judged as complete response if the tumor was completely regressed, partial response if it was partially regressed, and no response if no change in the tumor was visualized after IAC. Local consolidation with thermotherapy or cryotherapy to each tumor was not provided. Additional treatments and their reasons were recorded.

RESULTS

Of 190 children with retinoblastoma evaluated at the Ocular Oncology Service at Wills Eye Institute during this

Table 1. Characteristics of Patients Receiving Intra-arterial Chemotherapy for Retinoblastoma

Demographic Characteristic			Involved Eye at Time of Treatment					
Patient No./ Age, mo/ Race/Sex	Laterality of RB	Opposite Eye Status	Involved Eye	ICRB Group	Reese-Ellsworth Classification	Iris Neovascularization	Neovascular Glaucoma	Vitreous Hemorrhage
1/14/AA/M	B	Regr RB	L	[a]	[a]	No	No	No
2/10/W/F	U	NI	L	E	Vb	No	No	Yes
3/74/W/M	B	Regr RB	R	[a]	[a]	Yes	No	No
4/31/W/M	U	NI	L	E	Vb	No	No	No
5/25/W/M	U	NI	R	E	Vb	Yes	No	Yes
6/14/W/M	U	NI	R	D	IVa	No	No	No
7/23/W/F	U	NI	L	E	Vb	Yes	No	No
8/22/W/F	U	NI	L	C	IIIb	No	No	No
9/22/A/M	U	NI	L	E	Vb	Yes	Yes	No
10/10/W/M	B	Regr RB	R	[a]	[a]	No	No	No
11/14/H/F	B	Enuc	R	[a]	[a]	No	No	No
12/21/W/F	U	NI	L	E	Vb	Yes	Yes	No
13/13/W/F	U	NI	L	D	IVa	No	No	No
14/13/W/M	U	NI	R	D	IVa	No	No	No
15/17/W/M	U	NI	R	D	IVa	No	No	No
16/18/A/F	U	NI	R	C	IIIb	No	No	No
17/4/W/M	U	NI	L	D	IVa	No	No	No

Abbreviations: A, Asian; AA, African American; B, bilateral; Enuc, enucleation; H, Hispanic; ICRB, International Classification of Retinoblastoma; L, left; ; NI, normal; RB, retinoblastoma; Regr, regressed; R, right; U, unilateral; W, white.

[a] There was recurrence after systemic chemotherapy, so the globe was not suitable for classification.

Table 2. Summary of Globe Response to Intra-arterial Chemotherapy for Retinoblastoma

	IAC Procedure				Follow-up			
Patient No.	Treatment[a]	Reason for IAC	IAC Procedures, No.	Chemotherapy Agent	Main Tumor Response	Additional Treatment (mo After IAC)	Reason for Additional Treatment	Total Follow-up From IAC, mo
1	S	Recurrence after CRD	3	M, C	CR	No	NA	20
2	P	Refused Enuc	2	M, C	CR	Enuc (4)	Vitreous hemorrhage and NVG	19
3	S	Recurrent VS, AC seeds after CRD	4	M, C	CR	Enuc (6)	Recurrent VS, AC seeds	18
4	P	Refused Enuc	3	M, C	CR	EBRT (4)	Persistent VS	18
5	P	Refused Enuc	4	M, C	CR	No	NA	17
6	P	Refused Enuc	1	M, C	CR	No	NA	16
7	P	Refused Enuc	2	M	CR	Enuc (3)	Persistent VS, SRS	14
8	P	Refused Enuc	2	M	CR	No	NA	14
9	P	Refused Enuc	3	M	CR	Enuc (7)	Persistent NVG and vitreous hemorrhage	13
10	S	Recurrence after CRD	2	M	CR	No	NA	12
11	S	Recurrence after CRD	1	M	PR	EBRT (2) and Enuc (8)	Recurrent RB	10
12	P	Refused Enuc	2	M	PR	Enuc (3)	Persistent RB	9
13	P	Refused Enuc	3	M	CR	Plaque (5)	Recurrent SRS	9
14	P	Refused Enuc	1[b]	NA[b]	NA[b]	NA[b]	NA[b]	6
15	P	Refused Enuc	1	M	CR	No	NA	3
16	P	Refused Enuc	2	M	CR	No	NA	2
17	P	Refused Enuc	2	M	CR	No	NA	2

Abbreviations: AC, anterior chamber; C, carboplatin (30 mg); CR, complete response with no viable tumor; CRD, chemoreduction (6 cycles of vincristine sulfate, etoposide, and carboplatin); EBRT, external beam radiotherapy; Enuc, enucleation; IAC, intra-arterial chemotherapy; M, melphalan (5 mg); NA, not applicable; NVG, neovascular glaucoma; RB, retinoblastoma; P, primary; PR, partial (incomplete) response with residual viable tumor; S, secondary; SRS, subretinal seeds; VS, vitreous seeds.

[a] Secondary treatment indicates failure of other therapy.

[b] The procedure was aborted because of anomalous internal carotid anatomy and carotid spasm.

2-year period, 17 (9%) were treated with IAC. Seventeen eyes of 17 patients with retinoblastoma were treated with IAC using 38 catheterizations of the ophthalmic artery for delivery of chemotherapy (**Table 1** and **Table 2**). The mean patient age at IAC was 20 months (range, 4-74 months). All catheterizations were unilateral. The IAC was performed as primary in 13 cases and secondary (following failed other therapies) in 4 cases. Of the 13 primary cases, all were unilateral and the eyes were classified by the International Classification of Retinoblastoma as group C (n=2), group D (n=5), or group E (n=6) and by the Reese-Ellsworth classification as group IIIb (n=2), group IVa (n=5), group IVb (n=0), group Va (n=0), or group Vb (n=6). Of the 4 secondary cases, 1 patient had

Table 3. Specific Tumor Features Before Intra-arterial Chemotherapy for Retinoblastoma

Patient No.	Main RB		Quadrants Involved, No.			
	Base, mm	Thickness, mm	Subretinal Fluid	SRS	VS	AC Seeds
1	18	8.7	3	3	0	0
2	16	6.5	0	1	4	0
3	10	3.0	0	0	4	2
4	14	5.5	0	0	3	0
5	20	12.5	4	4	4	0
6	14	7.3	3	1	0	0
7	22	13.0	0	4	3	0
8	16	6.5	4	1	0	0
9	22	11.2	4	4	2	0
10	20	9.4	1	0	2	0
11	12	4.5	1	2	0	0
12	24	17.4	4	0	0	0
13	20	12.0	4	2	2	0
14	20	8.1	4	3	0	0
15	20	9.5	0	0	3	0
16	12	9.0	2	1	0	0
17	20	10.0	4	1	0	0
Mean (median)	17.6 (20)	9.1 (9.0)	2.2 (3)	1.6 (1)	1.6 (2)	0.1 (0)

Abbreviations: AC, anterior chamber; RB, retinoblastoma; SRS, subretinal seeds; VS, vitreous seeds.

Table 4. Specific Tumor Features After Intra-arterial Chemotherapy for Retinoblastoma

Patient No.	Main RB Size and % Change				TR or PR Requiring Further Other Therapies/Quadrants Involved, No.				
	Base, mm	Base Reduction, %	Thickness, mm	Thickness Reduction, %	Main RB	Subretinal Fluid	SRS	VS	AC Seeds
1	13	–28	2.4	–72	0	4	0	0	0
2	13	–19	6.5	0	0	0	0	0	0
3	5	–50	2.5	–17	0	1	0	TR/4	TR/3
4	10	–29	1.0	–82	0	0	0	PR/2	0
5	10	–50	6.5	–48	0	0	0	0	0
6	8	–43	3.0	–59	0	0	0	0	0
7	16	–27	4.7	–64	0	4	PR/3	PR/3	0
8	12	–25	2.1	–68	0	0	0	0	0
9	13	–41	5.0	–55	0	4	0	0	0
10	17	–15	6.0	–36	0	0	0	0	0
11	8	–33	3.0	–33	TR	1	0	0	0
12	22	–8	15.6	–10	PR	4	0	0	0
13	16	–20	4.3	–64	0	0	TR/2	0	0
14	NA[a]	NA[a]	NA[a]	NA[a]	NA[a]	NA[a]	NA[a]	NA[a]	NA[a]
15	12	–40	3.6	–62	0	0	0	0	0
16	7	–42	2.0	–57	0	0	0	0	0
17	8	–60	5.0	–50	0	0	0	0	0
Mean (median)	11.9 (12)	–33 (–31)	4.6 (4.0)	–49 (–56)	0 (0)	1.1 (0)	0.3 (0)	0.6 (0)	0.2 (0)

Abbreviations: AC, anterior chamber; NA, not applicable; PR, partial response; RB, retinoblastoma; SRS, subretinal seeds; TR, tumor recurrence; VS, vitreous seeds.

[a]The procedure was aborted because of abnormal carotid loop anatomy and carotid spasm.

the opposite eye enucleated and this was her only remaining eye. Catheterization was successful in 37 of 38 attempts. The failed catheterization was in 1 patient with anomalous internal carotid artery; he was subsequently treated with systemic chemoreduction.

Of the treated 16 eyes, the tumor features at the time of IAC included a median retinoblastoma basal dimension of 20 mm and a median retinoblastoma thickness of 9.0 mm. Additional features included the presence of vitreous seeds (9 eyes [56%]), subretinal seeds (11 eyes [69%]), anterior chamber seeds (1 eye [6%]), retinal detachment (11 eyes [69%]), iris neovascularization (5 eyes [31%]), neovascular glaucoma (2 eyes [12%]), and vitreous hemorrhage (2 eyes [12%]) (Table 1, Table 2, **Table 3**, and **Table 4**). In all cases, the family was offered enucleation as an alternative to IAC.

Following IAC, the main retinoblastoma showed complete response in 14 cases (88%), partial response in 2 cases (12%), and no response in 0 cases (**Figure 1**, **Figure 2**, and **Figure 3**). The main tumor regressed to a median of 31% in basal dimension and 56% in thickness, and all were type III regression (partially calci-

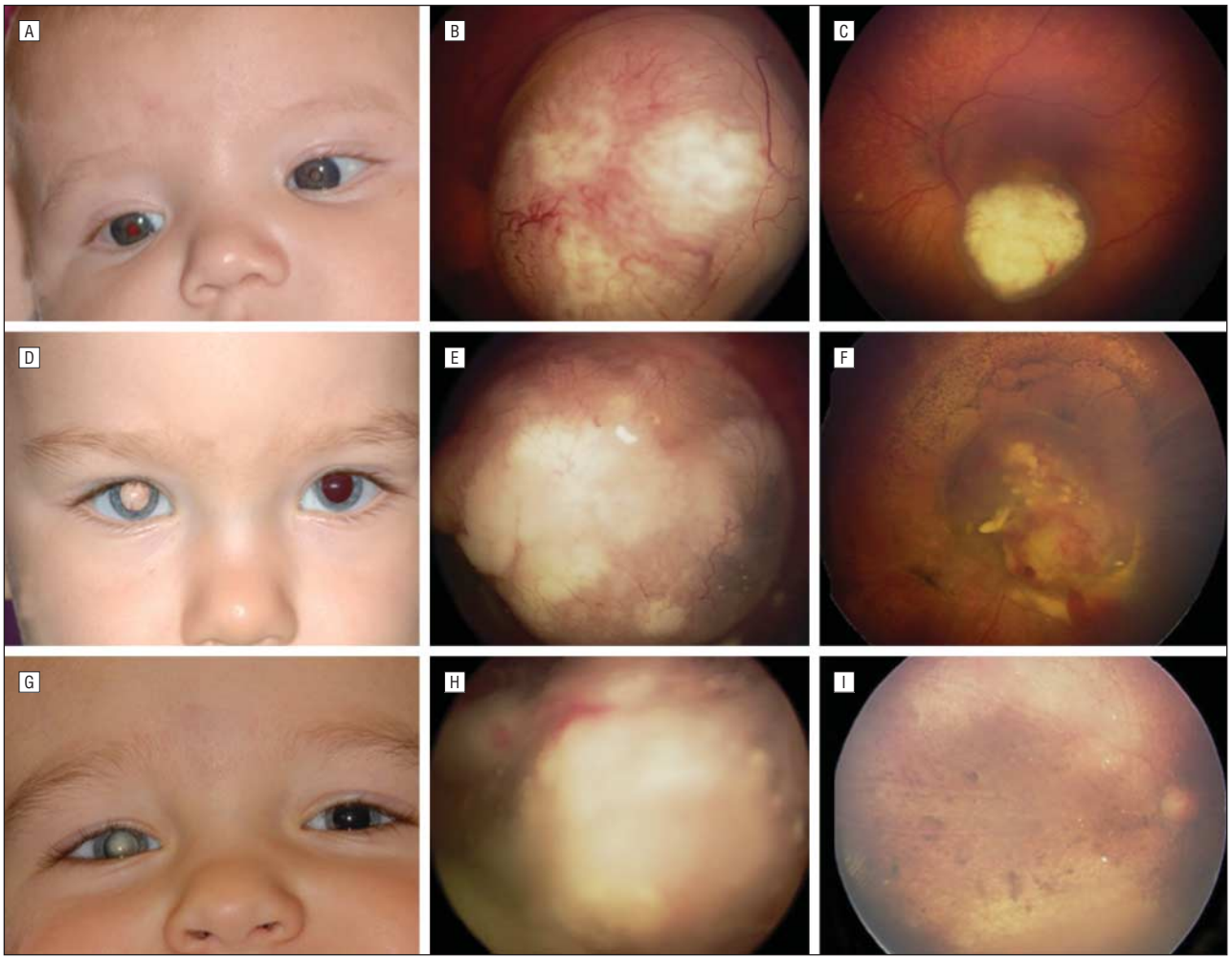

Figure 1. Complete response from intra-arterial chemotherapy for retinoblastoma. A 4-month-old boy had retinoblastoma (A), showing leukokoria in the left eye from a large macular retinoblastoma (B) with complete response after 1 dose of intra-arterial chemotherapy (C). A 17-month-old boy had retinoblastoma (D), showing leukokoria in the right eye from a large macular retinoblastoma (E) with surrounding extensive vitreous seeds noted inferotemporally; following 1 dose of intra-arterial chemotherapy, the retinoblastoma regressed completely (F) and the vitreous seeds regressed, leaving old and fresh vitreous blood. A 25-month-old boy (G) had advanced retinoblastoma and extensive vitreous seeding obscuring the entire fundus of the right eye (H); following 4 doses of intra-arterial chemotherapy, the tumor and vitreous seeds showed complete response (I) that has remained stable for 16 months.

fied). Of those eyes that showed initial complete tumor response and were followed up for a minimum of 1 year (up to nearly 2 years), complete response was maintained in all 10 eyes (100%). Of the 12 eyes managed with IAC as primary treatment, globe salvage was achieved in 8 (67%) and failure occurred in 4 (33%). Globe salvage was achieved in 2 of 2 group C eyes (100%), 4 of 4 group D eyes (100%), and 2 of 6 group E eyes (33%). Of the 4 eyes managed with IAC as secondary treatment after failure of other measures, globe salvage was achieved in 2 (50%).

Eleven of 16 eyes had subretinal seeds at the initial visit, and the subretinal seeds involved 1 to 4 quadrants (mean, 2.2 quadrants; median, 2 quadrants). Following IAC, complete response with complete regression of subretinal seeds was found in 9 eyes (82%), partial response was found in 1 eye (9%), and recurrence was found in 1 eye (9%). Nine of 16 eyes had vitreous seeds at the initial visit, and the vitreous seeds involved 2 to 4 quadrants (mean, 3.0 quadrants; median, 3 quadrants). Following IAC, complete response of vitreous seeds was observed in 6 eyes (67%), partial response was observed in 2 eyes (22%), and recurrence was observed in 1 eye (11%). The 2 eyes with partial response were further treated with external beam radiotherapy in 1 case and enucleation in 1 case. In the single case of anterior chamber seeds at the initial visit, initial complete regression was noted but recurrence in the form of anterior chamber and vitreous seeds was found at 6 months, necessitating enucleation despite 4 cycles of IAC.

Iris neovascularization regressed in 4 eyes (80%) and progressed to neovascular glaucoma in 1 eye (20%). In the 11 eyes with retinal detachment, the fluid involved 2 to 4 quadrants (mean, 3.5 quadrants; median, 4 quadrants). In 6 cases, the retinal detachment involved the entire fundus. Following IAC, the retinal detachment showed complete resolution to flat retina in 7 eyes (64%), partial resolution in 1 eye (9%), and no resolution in 3 eyes (27%). Of the 6 eyes with total retinal detachment, complete resolution with retinal flattening was observed in 4 (67%) following IAC.

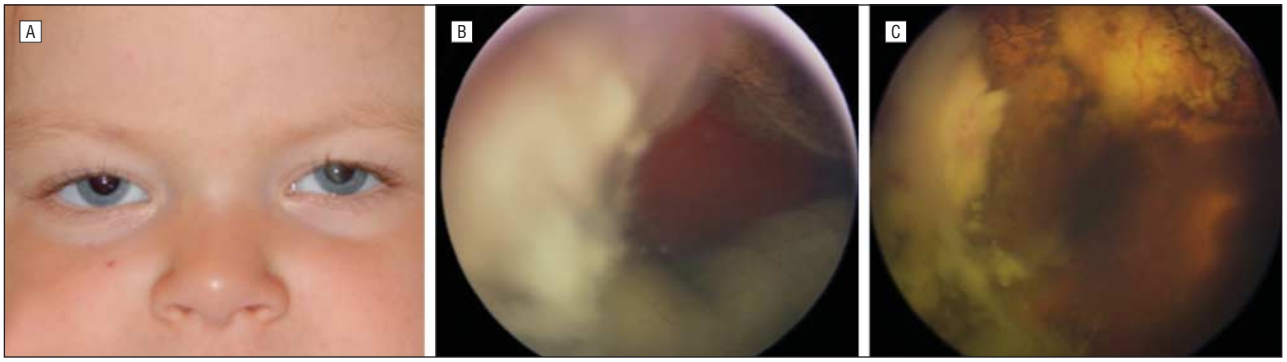

Figure 2. Partial response from intra-arterial chemotherapy for retinoblastoma. A 23-month-old girl had mild leukokoria (A) from advanced retinoblastoma with vitreous and subretinal seeding in the left eye (B), only sparing the fovea; following 1 dose of intra-arterial chemotherapy, the tumor and vitreous seeds showed partial response (C) with residual viable vitreous and subretinal seeds necessitating enucleation.

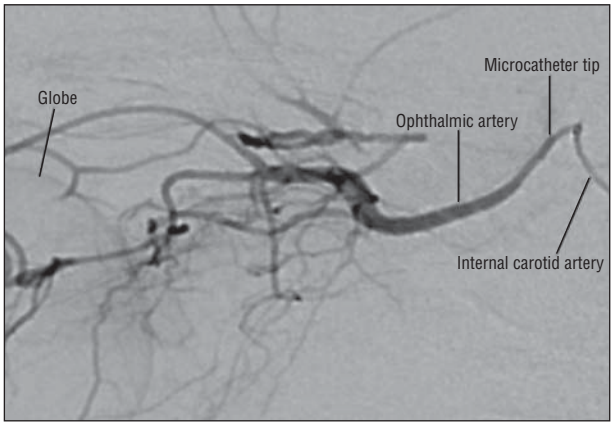

Figure 3. A cerebral angiogram (lateral view) shows superselective catheterization with the microcatheter tip in the proximal ophthalmic artery for delivery of chemotherapy to the globe.

There was tumor recurrence in 3 globes (19%) in the form of solid tumor in 1 (6%) case that showed partial response, subretinal seeds in 1 (6%), and vitreous or anterior chamber seeds in 1 (6%). Enucleation was necessary in 6 cases for reasons of recurrent tumor or seeds (n=2), partial response with incompletely controlled tumor or seeds (n=2), and neovascular glaucoma or vitreous hemorrhage (n=2). External beam radiotherapy was necessary in 2 cases, one with partial response of vitreous seeds and the other with partial response of main tumor. Plaque radiotherapy was used for 1 case of recurrent subretinal seeds.

The systemic and ocular complications of IAC for retinoblastoma are discussed in a separate article.[19] No patients developed metastasis, second cancer, or pinealoblastoma. No patients developed neurological defect, internal carotid artery occlusion, femoral artery occlusion, or stroke.

COMMENT

Intra-arterial chemotherapy for retinoblastoma is a novel, precise, technologically challenging method for delivery of chemotherapy to the eye. The rationale for delivery of chemotherapy by an intra-arterial route is to provide a higher local concentration and thereby achieve a greater biological effect at the site of interest while minimizing systemic effects. Preliminary studies have reported the efficacy and, to some extent, the safety of this approach.[15,20,21]

In this series, we contribute further to our understanding of tumor control with IAC. As with most new chemotherapy techniques, advanced disease is initially treated to define the limitations of a therapy. In this series, most patients (14 of 16 [88%]) had advanced group D or E retinoblastoma, all of whom were offered enucleation as an alternative therapy to IAC. In this small series, all eyes classified as group C or group D were successfully treated with IAC without need for enucleation or external beam radiotherapy. These findings superficially appear more successful than results from systemic intravenous chemoreduction, whereby success (globe salvage and avoidance of external beam radiotherapy) was achieved in 90% of group C eyes and 44% of group D eyes.[7] However, it should be realized that the IAC data are more preliminary, with a shorter follow-up period and the study cohort being much smaller than previously reported with chemoreduction.[7] Regression to a type III (partially calcified) remnant following IAC was similar to regression patterns found following chemoreduction.[22]

Advanced group E eyes show a relatively high failure rate with both IAC and intravenous chemoreduction.[23] In this series, group E eyes showed failure requiring enucleation in 4 cases (67%) for reasons of tumor recurrence (n=1), partial response of vitreous and subretinal seeds (n=1), and neovascular glaucoma or vitreous hemorrhage (n=2). In comparison, chemoreduction alone has been shown to provide tumor control in only 25% of group E eyes, but this was improved to 83% control if prophylactic low-dose external beam radiotherapy was additionally given.[23]

Of the 10 eyes with retinoblastoma with initial complete response to IAC and followed up for a minimum of 1 year, tumor control was lasting in all cases with no retinal tumor recurrence. However, seed recurrence can be a problem. Of the 11 eyes with subretinal seeds at the initial visit, complete response was achieved in 9 (82%), partial response occurred in 1 (9%) (managed with enucleation), and recurrence was found in 1 (9%) (managed with plaque radiotherapy). Of the 9 eyes with vitreous seeds at the initial visit, complete response was achieved

in 6 (67%), partial response was found in 2 (22%) (managed with external beam radiotherapy in 1 case and enucleation in 1 case), and recurrence was observed in 1 (11%) (managed with enucleation). Chemotherapy likely reaches subretinal seeds from both choroidal and retinal blood flow, contributing to effective control in 82%. There is no direct blood flow into the vitreous, but leakage of the chemotherapeutic agent through retinal vessels likely contributed to control of the vitreous seeds, successful in 67%. The single patient with anterior chamber seeding showed initial response but later recurrence with ultimate enucleation.

A concern with single-agent chemotherapy is the possibility of resistance with long-term recurrence. There has been greater experience with multiagent intravenous chemotherapy (chemoreduction) for retinoblastoma, and a review of published results indicates that tumor seed recurrence is the most common reason for ultimate failure and enucleation.[24,25] In an analysis of 158 eyes with retinoblastoma treated with intravenous chemoreduction, recurrent active vitreous seeds were found in 50% and subretinal seeds were found in 62% at 3 years, with little further recurrence at 5 years.[24] In that large cohort, most recurrences were detected by the 3-year point. In an analysis of single-agent intravenous chemoreduction with carboplatin alone for management of retinoblastoma in 43 eyes, tumor recurrence was found in 67%, necessitating enucleation or external beam radiotherapy.[25] Hence, in this current small cohort of eyes treated mostly with single-agent IAC, our results are preliminary as most patients were followed up for 1 to 2 years and we anticipate a risk for recurrence. Cautious monitoring for 3 to 5 years will be necessary.

Another concern with locally delivered single-agent chemotherapy is the lack of control of potential metastatic disease, most often associated with advanced retinoblastoma. None of our patients developed metastasis. Of the 6 eyes that were enucleated, none had high-risk features, but important histopathologic findings will be reported in a separate article.[26]

The limitations of this study include the small cohort of 16 treated eyes and relatively short follow-up, with only 10 eyes having 1 to 2 years of follow-up. We anticipate that longer follow-up will provide more information regarding lasting tumor response. However, at least in the short-term, this technique appears favorable for group C and D eyes.

In summary, in this article we describe retinoblastoma and tumor seed control with IAC. Several benefits of IAC should be realized, including the small chemotherapy dose, few necessary sessions, and 1-day delivery. The ideal dose and number of cycles have not yet been determined, but we have found 2 to 3 cycles satisfactory for most tumors. Despite the favorable initial results, several issues regarding IAC should be addressed in the future. These include the difficulty of the IAC technique, vascular injury or toxic effects, end-organ ischemia, and radiation exposure.[27] This technique is challenging and requires a physician experienced in interventional neuroradiology or endovascular neurosurgery and comfortable with cannulation into the brain of a toddler or infant. There are assumed risks for neurovascular injury, so this technique should be limited to select, experienced centers until the full value and limits of this approach are realized. In a separate article, we address the ocular and systemic toxic effects of this approach.[19] Until the full spectrum of benefits and risks of IAC is understood, we continue to use this technique with caution.

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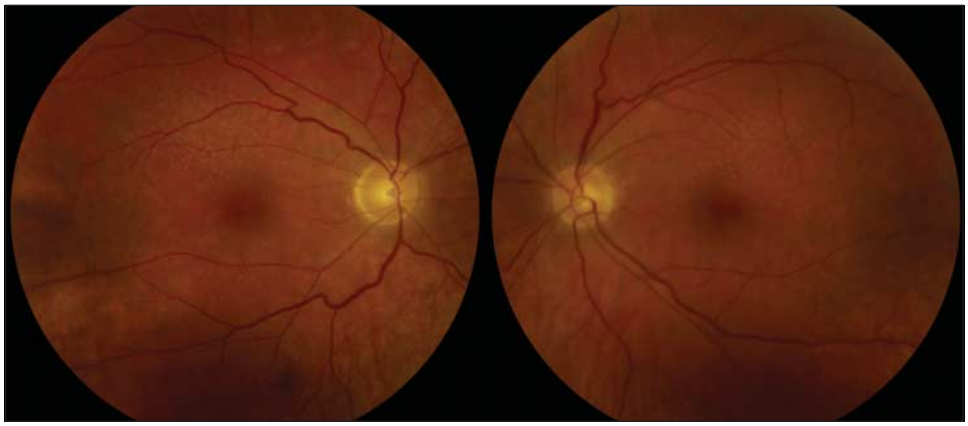
Archives Web Quiz Winner

Congratulations to the winner of our June quiz, Juan David Arias Aristizabal, Fellow of Retina and Vitreous of Clinica Oftalmologica Centro Caracas, Arevalo Coutinho Foundation for Ophthalmology Research, Caracas, Venezuela. The correct answer to our June challenge was spinocerebellar ataxia type 1. For a complete discussion of this case, see the Research Letters section in the July Archives (Thurtell MJ, Biousse V, Newman NJ. Rod-cone dystrophy in spinocerebellar ataxia type 1. *Arch Ophthalmol*. 2011;129[7]: 956-958).



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