Intra-arterial Chemotherapy for Retinoblastoma

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Objective: To describe treatment complications following intra-arterial chemotherapy (IAC) for retinoblastoma.

Methods: A retrospective interventional series of ophthalmic artery cannulation for IAC injection (3 planned sessions at 1-month intervals) was undertaken. Thirty-eight catheterizations of 17 eyes of 17 patients were performed from September 2008 to September 2010. Fluoroscopy of the ophthalmic artery was performed before and immediately after treatment. Heparin was given during the procedure and aspirin (40 mg) was given orally for 1 week. The treatment complications were determined.

Results: Only 17 of 190 children were selected for treatment with IAC during this period. Following successful ophthalmic artery cannulation in 16 cases, there was no evidence of metastasis, stroke, brain injury, or persistent systemic toxic effects. Fluoroscopy demonstrated patent ophthalmic artery immediately before and after IAC injection in each case. Following therapy, orbital and adnexal findings at 1 month included eyelid edema (n=13), blepharoptosis (n=10), cilia loss (n=1), and orbital congestion with temporary dysmotility (n=12). These findings resolved within 6 months in all cases. Following therapy, vascular findings included ophthalmic artery stenosis (permanent in 3 cases, temporary in 1 case), confirmed on fluoroscopy in 3 cases. Concomitant central or branch retinal artery occlusion was noted (permanent in 2 cases, temporary in 1 case). Subtle retinal pigment epithelial mottling in 9 cases that slowly evolved to later-onset underlying choroidal atrophy in 5 cases was noted.

Conclusions: Treatment with IAC for retinoblastoma can lead to mild and severe short-term ocular complications, including eyelid edema as well as potentially blinding vascular obstruction. This procedure should be used with caution.

obstruction. They described the safety of this technique with hundreds of cannulations and no sign of stroke, but detailed data regarding tumor control and treatment complications were lacking in their articles.9,10

Gobin and Abramson11 and Gobin et al12 in the United States devised a refined approach with direct catheter entry into the proximal portion of the ophthalmic artery for delivery of chemotherapy to the eye. With this approach, Abramson et al13,14 provided initial observations of impressive tumor response, even in eyes with advanced retinoblastoma. Regarding treatment complications, they observed that “the only adverse ophthalmic findings were occasional transient lid edema, forehead hyperemia, and loss of nasal lashes.”13 However, other information (from the same group of investigators) remarked on more serious complications including femoral artery occlusion for 1 week and leukopenia in fewer than 10%, and they identified that “there were 4/46 severe ocular complications which consisted of avascular retinopathies resulting in blindness.”12 Further investigation of published reports has revealed illustrations documenting outstanding tumor regression but with visible complications of diffuse retinal pigment epithelial (RPE) alterations and choroidal ischemia.13

We have described our experience with somewhat impressive short-term control of retinoblastoma using IAC in selected cases.16 Herein, we delineate the ocular and systemic complications using this technique.

### METHODS

Institutional review board permission was obtained for this ongoing prospective 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. Patients and parents were informed of the risks of ophthalmic artery cannulation, including brain or orbital hemorrhage, infection, and inflammation, visual loss, loss of the eye, anaphylaxis, stroke, and death. Patients and parents were 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, or orbit or distant metastasis.

The details of the technique of examination and follow-up are described in a separate article.18 Each patient was examined initially in the office and then under anesthesia by one of us (C.L.S.) with clinical evaluation and large fundus drawings, fundus photography, and fluorescein angiography of all tumors in each eye. The IAC was performed under anticoagulation with intravenous heparin (75 IU/kg) and has been described previously.16,17 Chemotherapy diluted in 30 mL of saline was delivered using a pulsatile, nonlaminated technique manually over 30 minutes. The selected chemotherapy drug was melphalan (5 mg) in all cases and additional carboplatin (30 mg) was used in cases 1 through 6 based on previously documented efficacy.18 Carboplatin was later discontinued after observations of ophthalmic or retinal vascular attenuation as platinum-based drugs have been recognized to have a sclerosing effect.19 A postinfusion arteriogram was taken to confirm patency of the ophthalmic artery. Following catheter withdrawal, oral aspirin (40 mg) was delivered for 2 weeks. Follow-up ophthalmic examination was provided at 1 month, and a second treatment with IAC was performed as necessary and then repeated 1 month later if necessary. Thereafter, ophthalmic examination was provided every 2 to 3 months. Documentation was made in each case with large fundus drawing, fundus photography with a Retcam camera (Massie Industries, Dublin, California), fluorescein angiography, and electroretinography.

All data were collected in a retrospective fashion. Each patient was evaluated for age at diagnosis (months), race (African American, Asian, Hispanic, white), sex (male, female), and hereditary pattern (sporadic, familial). Before and following IAC, each patient was assessed for metastatic disease, second cancer, pinealoblastoma, and damage to the central nervous system manifesting as neurologic deficit or stroke. The orbit and adnexa were evaluated for permanent or temporary eyelid edema, blepharoptosis, forehead erythema, eyelash loss, and dysfunction of the extraocular muscles. The globe was assessed for patency of the vascular flow to the eye including the internal carotid artery, ophthalmic artery, central retinal artery, branch retinal artery, retinal venous drainage, and choroidal vascular bed. The fundus was evaluated for the status of the retina, RPE, and optic nerve. New or preexisting neovascularization of the iris with or without neovascular glaucoma was recorded.

| RESULTS |

Seventeen patients were included in this study on IAC for retinoblastoma. The mean patient age at IAC was 20 months (range, 4-74 months). Cannulation into the proximal region of the ophthalmic artery was possible in 16 patients. In 1 patient, cannulation was not possible owing to internal carotid artery anomalous pattern with a 360° loop and severe spasm during the procedure. This patient was subsequently treated with intravenous chemoreduction. A total of 37 of 38 catheterizations of the ophthalmic artery were successful for delivery of chemotherapy. All catheterizations were unilateral. The mean number of catheterizations per eye for control of retinoblastoma was 2.25 (median, 2; range, 1-4). Following IAC, complete response of the main tumor was achieved in 14 cases (88%), partial response was found in 2 cases (12%), and no response was observed in 0 cases.16 Globe classification, tumor features, treatment parameters, and tumor control for this cohort of 17 patients are detailed in a separate article.16

The systemic and ocular complications of IAC for retinoblastoma are listed in Table 1 and Table 2 (Figures 1, 2, 3, 4, and 5). No patients developed metastasis, second cancer, or pinealoblastoma during a mean of 13 months of follow-up. No patients developed neurologic defect, internal carotid artery occlusion, femoral artery occlusion, or stroke. One patient with anomalous internal carotid artery had a spasm during cannulation and the procedure was discontinued. Transient cytopenia was present in 6 cases with spontaneous recovery in all cases without the need for transfusion.

Ophthalmic adverse effects included eyelid edema (n = 13), blepharoptosis (n = 10), and cilia loss (n = 1) (Figure 1). There were no cases of forehead erythema. Congested orbit with temporary extraocular muscle dysfunction was found in 12 eyes. These external findings
resolved in every case by 2 months, but blepharoptosis resolved more slowly over 4 to 6 months. In 1 case, the dysmotility respected the distribution of the third cranial nerve and persisted for 4 months. Occlusive vasculopathy was noted in the ophthalmic artery in 4 cases and diagnosed by funduscopy in 3 of those cases. In 1 case,
preexisting mild vitreous hemorrhage worsened following IAC and there was no view of the fundus. However, on arteriography, the ophthalmic artery showed stenosis and further therapy was discontinued. Of those with clinically visible ophthalmic artery occlusion, the main fundus features included central retinal artery obstruction (n=1), multifocal branch retinal artery obstruction (n=3), and evidence of choroidal atrophy (n=2). In 1 case, the ophthalmic artery obstruction and related branch retinal artery obstruction resolved completely within 1 month. In 1 case, the choroid was camouflaged by extensive confluent subretinal seeding.
There were no visible emboli in any artery on ophthalmoscopy or fluorescein angiography. On fluorescein angiography, the 3 cases of posttreatment central retinal artery obstruction and branch retinal artery obstruction showed slow perfusion of the attenuated retinal arteries. Despite the poor flow, no iris neovascularization, neovascular glaucoma, or pain developed. One patient who initially had mild vitreous hemorrhage (presumably from pretreatment retinal neovascularization) eventually developed dense vitreous hemorrhage and neovascular glaucoma and required enucleation. Of the 5 eyes with iris neovascularization before treatment, only 1 had persistent neovascularization after treatment (requiring enucleation) and the remainder showed resolution of neovascularization with tumor regression and resolution of the retinal detachment.

Following IAC, attenuation of the choroidal vascular bed was found in 5 cases. Of 13 patients followed up for 6 months or longer, choroidal atrophy was noted in 4 of the 9 patients (44%) in whom a clear view of the choroid was obtained. This finding was noted in 1 of 3 patients followed up for less than 6 months. This finding initially manifested as focal or diffuse RPE mottling with gradual loss of the choriocapillaris and, in some cases, the larger choroidal vessels. Following IAC, RPE mottling was detected in 9 eyes and with gradual progression over time (Figure 3 and Figure 5). In 3 eyes, there was poor to no view of the RPE due to overlying vitreous hemorrhage or confluent subretinal seeds.

**COMMENT**

We have used IAC for longer than 2 years in the management of selected cases of retinoblastoma. We have observed both complete response and less impressive partial response of retinoblastoma. We have used this therapy for primary as well as recurrent retinoblastoma. In a separate article describing our 2-year experience with this approach, we found 100% tumor control for primary retinoblastoma in group C and D eyes and 33% control for group E eyes. However, we use this new therapy with caution because of the potential for local ocular toxic effects.
Several benefits of IAC should be highlighted, including the localized chemotherapy injection, few necessary sessions (approximately 2 doses), 1-day delivery, and systemic tolerance. On the other hand, several concerns about IAC should be realized, including the potential for vascular injury or toxic effects, end-organ ischemia, and fluoroscopic-related radiation exposure.

Following IAC, some mild and some severe short-term effects should be anticipated. The mild short-term effects included eyelid edema, blepharoptosis, and orbital congestion, sometimes with temporary dysmotility. These findings were common and typically resolved within a few months, leaving minimal or no residua and without need for surgical repair. In 1 case of dysmotility, the features were consistent with transient oculomotor (third nerve) palsy. This finding has been previously observed in 3 of 7 patients (43%).

The more serious short-term effects involved acute and chronic vascular insult, particularly to the ophthalmic, retinal, and choroidal vessels. Ophthalmic artery stenosis or obstruction manifested with pale optic nerve, reduced retinal blood flow, and patchy reduction in choroidal blood flow. In our series, occlusion or stenosis of the ophthalmic artery was observed in 4 cases, with resolution in 1 case by 1 month of follow-up. In 3 cases, the stenosis was confirmed under fluoroscopy at attempted catheterization for a repeated dose. No affected eyes developed neovascularization of the disc or retina, neovascular glaucoma, or pain or required enucleation for this finding. The specific pathogenesis of the vascular insult remains unknown, but it could be secondary to catheter-related injury to the endothelium, chemotherapy toxic effects on the vessel or specifically the endothelium, or embolization from foreign body contamination or chemotherapy precipitation. There were no clinically visible emboli in any case. The prefluoroscopy and postfluoroscopy findings showed that the ophthalmic artery was patent at the time of IAC in all cases, suggesting a lack of catheter-related dissection, trauma, or embolism. The onset of ophthalmic and retinal arterial obstruction was often evident by the 1-month follow-up, whereas the choroidal vascular atrophy generally took several months to become apparent, showing slow progression. These findings might suggest chemotherapy toxic effects.

This finding of ischemia has been previously recognized as a serious short-term risk of this therapy. Gobin et al noted that 4 of 46 eyes (9%) had "severe ocular com-

**Figure 4.** Transient ophthalmic artery obstruction following intra-arterial chemotherapy for retinoblastoma in case 15. Macular retinoblastoma (A) with retinal detachment showed enhancement on fluorescein angiography (B) and good peripheral retinal perfusion. Following 1 cycle of intra-arterial chemotherapy, there was ophthalmic artery stenosis with poor retinal and choroidal perfusion clinically (C) and angiographically (D). Retinal perfusion improved to normal by 2 months’ follow-up and no further chemotherapy was delivered.
plications which consisted of avascular retinopathies resulting in blindness.12 We speculate that this finding could be overlooked in some cases, particularly if fluorescein angiography is not used. We perform fluorescein angiography at each session to confirm ocular blood flow. Occasionally, the retinal vessels appear intact clinically and the attenuation is detected only by fluorescein angiography. We encourage all centers using IAC to carefully study the ocular blood flow using fluorescein angiography. In comparison, our experience with intravenous chemoreduction in more than 500 children has revealed no similar incident of postchemotherapy ophthalmic, retinal, or choroidal ischemia.

In contrast to the abrupt finding of ophthalmic or retinal vascular obstruction, the choroidal ischemic process manifested more slowly, with patchy focal areas of subtle RPE alterations that gradually evolved over several months into RPE atrophy, then choriocapillaris and occasionally large choroidal vessel atrophy. The features of choroidal atrophy were mild in most cases. It is recognized that the presence of serous retinal detachment or even a large tumor base could lead to chronic underlying RPE alterations, but in these cases, the RPE atrophy has been diffuse in previously uninvolved areas.

The evolving sequence of diffuse, homogeneous choroidal atrophy might be suggestive of slow-onset involutional atrophy (Figure 3), perhaps from chemotherapy toxic effects more so than an acute embolic or traumatic event, which would more likely produce sector damage.

Scrutiny of previously published articles reveals printed illustrations showing choroidal atrophy that was not recognized by the authors.13,21 We speculate that subtle cases could be overlooked and this finding could be much more common than anticipated. Furthermore, we have examined in consultation children who were treated with IAC at other centers in whom choroidal atrophy was unequivocally evident over time. This finding can be subtle and delayed over several months.22 Munier et al22 identified sector choroidal atrophy as a particular concern in 15% of cases. The implications of choroidal atrophy on ultimate visual acuity in children could be profound. However, it should be realized that most of these eyes would have otherwise been enucleated and had complete loss of vision.

Intra-arterial chemotherapy has been used for other systemic malignant neoplasms, and the technique has been complicated by vascular toxic effects, similar to our experience with retinoblastoma. For example, Madaje-

![Figure 5. Nontransient ophthalmic artery obstruction following intra-arterial chemotherapy for retinoblastoma in case 6. Macular retinoblastoma (A) showed complete response following 1 cycle of intra-arterial chemotherapy (B). However, the intact nasal retina before treatment (C) showed broad choroidal atrophy at 1 year following treatment (D).](https://archopht.jamanetwork.com/)
wicz et al\textsuperscript{23} found IAC to be more beneficial for survival if delivered before rather than along with radiotherapy for glioblastoma multiforme. However, other trials showed contrasting findings.\textsuperscript{24,25} Grimson et al\textsuperscript{24} emphasized that IAC for brain malignant neoplasms could lead to dose-dependent eye pain, vision loss, and encephalopathy, particularly if the injection into the internal carotid artery was below the take-off of the ophthalmic artery. Shapiro et al\textsuperscript{23} compared IAC vs intravenous chemotherapy in 448 patients with malignant glioma and showed reduced survival for the IAC group plus related toxic effects of encephalopathy (9.5\%) and ipsilateral vision loss (15.5\%). Fortunately, we have not witnessed any evidence of toxic effects in the brain in our patients during this 2-year period.

For pediatric malignant neoplasms, IAC has been used for osteosarcoma. When used as a monotherapy, intra-arterial infusion of cisplatin appeared to be more effective against osteosarcoma than intravenous infusion.\textsuperscript{20} However, other reports showed that intra-arterial superiority was diminished when multiagent therapy was needed.\textsuperscript{27,28} One report entitled “Intraarterial Chemotherapy for Osteosarcoma: Does the Result Really Justify the Effort?” by Bielack et al\textsuperscript{28} highlighted the risks of this procedure. They indicated that the risks and discomforts of IAC for osteosarcoma were considerable, intractable pain occurred in more than 50\% of the infusions, and local complications of vasculopathic ischemic necrosis, thrombosis, infection, and neuropathy were found.

With regard to retinoblastoma, a major concern is the potential for metastatic disease, especially if the eye shows features of high-risk retinoblastoma with tumor invasion into the choroid or postlaminar optic nerve. Often this is not clinically apparent and is found only on histopathologic examination following enucleation.\textsuperscript{29–32} In a comprehensive histopathologic analysis of nearly 300 eyes, high-risk features were found in 18.5\% of cases, with retrolaminar optic nerve invasion in 10.4\% and massive choroidal invasion in 8.1\%.\textsuperscript{31,32} Eyes with high-risk features develop metastasis (leading to death) in 24\%, unless intervention with systemic intravenous chemotherapy is delivered, reducing the metastatic rate to 4\%.\textsuperscript{33} Intra-arterial chemotherapy is designed to selectively treat the eye and would likely be insufficient for remote subclinical metastatic disease. Over time, this could be a threat to the patient’s life prognosis. Fortunately, in our series, there was no evidence of metastatic retinoblastoma. However, we are aware of 3 cases of metastatic retinoblastoma from other centers using this technique.

The technique of IAC requires fluoroscopy for accurate guidance of the catheter. The cumulative radiation exposure with potential risk for toxic effects has been explored by Vijayakrishnan et al.\textsuperscript{34} They found doses of 19,173 mrad to the affected eye, 3533 mrad to the contralateral eye, and 5560 mrad to the brain. Other sensitive organs like thyroid, bone marrow, and gonads received a small dose far below the minimal toxic level, but the dose to the lens was possibly cataractogenic. They cautioned that fluoroscopic use should be minimized to avoid radiation-related toxic effects in these patients.

In summary, despite dramatic response of retinoblastoma to IAC\textsuperscript{1,6,13–16} there is concern for toxic effects from both chemotherapy and radiotherapy exposure. With this in mind, we cautiously use IAC for retinoblastoma in selected cases.

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