What’s New in Intra-Arterial Chemotherapy for Retinoblastoma?

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In 2006, we introduced modern intra-arterial chemotherapy [ophthalmic artery chemosurgery (OAC)] for retinoblastoma. Since then it has been adopted worldwide and performed in > 45 countries with > 200 peer-reviewed articles supporting its use. There are multiple reports on the technique, efficacy, and toxicity of this approach.

The technique we described has been adopted without modifications by all centers worldwide. In total, 80% of the time drug can be delivered directly into the ophthalmic artery and in the remaining 20% access is obtained via a modification of the original Japanese technique or through branches of the external carotid. It was the Japanese who chose to use melphalan and we then added the use of carboplatin and topotecan; today all patients worldwide are treated with combinations of these 3 drugs. As we advised, almost all centers worldwide are anticoagulating their patients with heparin during the procedure, filtering the melphalan, injecting drug in a pulsatile way and applying vasoconstrictive drops/spray into the nose and forehead (in the distribution of the supratrochlear artery). The procedure is an outpatient one and no procedural deaths have been reported worldwide. The mean number of treatments is just over 3 monthly infusions but success has been obtained with as little as one OAC treatment.

The efficacy of the procedure has been emphasized by all. More advanced eyes are salvaged than with radiation or multiagent systemic chemotherapy and the time to attain cure is shorter with intra-arterial chemotherapy. Both unilateral and bilateral patients can be treated with both naive or recurrent disease. For eyes with no vision, extinguished electroretinograms (ERG) and retinal detachments, some sight is recovered in almost a third of cases. Cures with OAC use far less
chemotherapy than when chemotherapy is given intravenously and it has further eliminated the need for external beam irradiation in the treatment of intraocular retinoblastoma. The technique has been used in both developed and developing countries with equal success.8

As expected, there is far less systemic toxicity with OAC as much smaller doses of the drug are used. Melphalan is not used systemically for intraocular retinoblastoma but the doses used for carboplatin and topotecan are ~1/30th that used systemically. Despite the tiny amounts of drug delivered by OAC, animal experiments show drug levels in the eye that are 100 times that obtained with intravenous use11; for reasons that are not known levels in the optic nerve are > 50 times that obtained in the eye itself.12,13 The melphalan dose delivered to the eye is just under 0.50 mg/kg and at that dose neutropenia is common but <1% of patients require transfusion of any blood product.14

In most cases, there is little ocular toxicity from OAC. Toxicity is mostly seen in centers when they first begin to use OAC and many centers have pointed out that their complication rate is under 5% once they master the technique.15 Transient periorbital edema is common but the hyperemia previously described in the distribution of the supratrochlear nerve is eliminated by the use of locally applied sympathomimetics during the procedure.16 Motility problems described in the literature seem to be inflammatory and resolve. There have been no anterior segment, lens, intraocular pressure, or ocular motility issues other than those already mentioned. Cataracts that have developed are thought to be related to the advanced disease, phthisis, retinal detachment, and intravitreal chemotherapy these children also receive. Even eyes with vitreous seeds are routinely saved as a result of the use of OAC as are most of the eyes with subretinal seeding.17 Even in experienced hands retinal toxicity can develop —presently thought to be in the 2% range. Whether this is drug toxicity or choroidal infarctions has been the subject of interest of many authors.18,19

Literally, overnight the retinoblastoma community has gone from enucleating nearly all eyes with extensive vitreous and/or subretinal seeding to salvaging > 80% of these eyes. The incidence of enucleation has dropped in some centers to near 5%.15 The impact on bilateral disease is even more striking. More eyes are salvaged with OAC than external beam irradiation or multiagent systemic chemotherapy.16 For naive eyes treated at the same time (tandem therapy), salvage rates of > 95% have been reported!20

A new reflex was discovered in children receiving OAC. When the catheter approaches the orifice of the ophthalmic artery profound decrease in tidal volume has developed in as many as 20% of children but fortunately it is well managed with intravenous epinephrine.21 Some centers pretreat children with IV epinephrine before the reflex develops.

Despite treating eyes with advanced intraocular retinoblastoma patient survival has been excellent. In a review of > 130 peer-reviewed
publications, no metastatic deaths were reported in >98% of papers. The world’s 5 largest centers combined their 10-year experience in treating unilateral and bilateral, naive and failed cases, and the incidence of death from metastatic disease was under 1%.22,23

Retinoblastoma patients with the genetic form of the disease are at high risk for developing second, nonocular cancers. Historically this develops in the range of 1% a year and more than half of these second cancers cause the death of the patient.24 Unfortunately, this risk is increased when children are exposed to external beam radiation (especially if delivered in the first year of life). OAC eliminates the use of radiation and thus eliminates the main cause of cancer-related deaths in these children. Secondary acute myelogenous leukemia, a problem for retinoblastoma patients who received multiagent systemic chemotherapy has not been reported to date but trilateral retinoblastoma still develops.25

There have been a number of newer observations on OAC and we will outline these newer findings below:

Immune function: multiagent systemic chemotherapy always impairs immune function. At times the impact is mild-grade 1 or 2 hematologic toxicity. The development of fever/neutropenia, however, adds significant anxiety, risk, cost, and complications when more severe toxicity develops. Hospitalization, blood cultures, antibiotics, and time away from school are just some of these effects and when severe the infections (or complications of treatment) can lead to permanent disabilities and even death. The cost of dealing with these complications exceeds the actual cost of the cancer treatment and drugs themselves. Because of routine impairment of immune function children receiving multiagent systemic chemotherapy are placed on Pneumocystis pneumonia (PCP) prophylaxis with daily antibiotics (bactrim) for years. In addition, almost all vaccines are withheld.

It was suspected that OAC had no/very rare effects on immune function because <1% of treated patients develop fever/neutropenia or require transfusion of any blood product.14 A recent study from our Institution confirmed that major markers of immune function are not affected by OAC so as a result children receiving OAC do not need PCP prophylaxis and are not given daily bactrim.26 In addition, they may receive all vaccines on normal schedule—an especially important feature since they are (monthly) exposed to other children with cancer and immune-compromised diseases in the clinic and hospital.

Growth and development: it is common for the growth of children to be slowed down while receiving systemic chemotherapy. Usually (but not always) growth catches up once the chemotherapy is stopped. This association has not been studied for systemic chemotherapy but has for OAC. Growth is not slowed down during OAC and in fact, children who have received systemic chemotherapy have accelerated growth when they then receive OAC.27
Retinal detachment: traditionally most eyes with total retinal detachment were enucleated as it was taught that return of vision was impossible and the cost, time, and potential side effects of treatment were not warranted in a blind eye. In addition, it was felt that even if the eye could be salvaged phthisis was inevitable. Multiple centers have challenged this age-old dogma. In fact, the majority of eyes with total retinal detachment treated with OAC reattach. Of the eyes that reattached, 13% reattached after the first OAC, 20% after the second OAC and 53% after the third OAC. Almost a quarter of the eyes with extinguished ERG’s at presentation had measurable ERG after treatment and 14% of eyes gained at least 25% of ERG function.

Choroidal invasion: blood flow to the choroid far exceeds blood flow to the retina and indeed more drug is delivered to the choroid than retina with OAC. In the past choroidal invasion has been near impossible to eliminate but recent studies have shown that choroidal invasion in retinoblastoma can be quickly and permanently eliminated with OAC alone.

Deletion children and downs children: although the evidence is scantily it is widely felt that children with gross chromosomal aberrations—such as children with trisomy 21 and retinoblastoma children with 13q deletion syndrome—handle systemic chemotherapy poorly. These children tolerate OAC easily and do not develop complications as a result, so OAC opens a group of patients to targeted chemotherapy who were previously enucleated because of fear of complications from systemic chemotherapy.

Bilateral retinoblastoma management: OAC has caused a complete change in the management of bilateral retinoblastoma (Table 1). Until the adoption of radiation, the only way to treat these children was bilateral enucleation. No eye was salvaged, no vision retained, and patient survival was 15%. When external beam irradiation was adopted it was Reese who popularized the concept of enucleating the more involved eye and radiating the less involved eye. In total, 25% of eyes were saved and patient survival was 77%. In the 1980s some patients with bilateral disease were radiated bilaterally—overall ocular survival was 75% and patient survival 83%. When systemic chemotherapy replaced radiation in the 1990s many eyes were still enucleated but of those treated without enucleation, ocular survival for advanced eyes was under 50% and patient survival was 93% to 97%. When both eyes were treated with OAC (tandem therapy) ocular survival reached an all-time high (91.5%—which includes primary enucleations) especially if you realize that 95% of eyes were treated and not enucleated.

New tumors: new, peripheral tumors commonly develop in patients with bilateral retinoblastoma despite treatment of existing tumors. Although this was first pointed out > 50 years ago in patients radiated, they develop with equal frequency following xenon arc photocoagulation, external beam irradiation, and single-agent or multiagent
| Year      | Treatment                               | Ocular Survival (%) | Metastatic Deaths (%) | Second Cancers                  |
|-----------|-----------------------------------------|---------------------|-----------------------|---------------------------------|
| <1900     | Bilateral enucleation                   | 0                   | 85                    | Unknown                         |
| 1950-1980 | Enucleate worse, radiate better         | 25                  | 23                    | 50%/50 y                        |
| 1980-1995 | Bilateral radiation                     | <50*                | 17                    | 50%/50 y                        |
| 1995-2006 | Systemic chemotherapy plus local        | <50*                | 4-7                   | Less radiation-related, more sAML |
| 2006-     | OAC                                     | 91.50               | 0                     | No RT/sAML, 3.9% pineal†         |

*Of all ICRb group D eyes seen.
†Unilateral patients with positive genetics and bilateral patients.
ICRb indicates International Classification of Retinoblastoma; OAC, ophthalmic artery chemosurgery; RT, radiation therapy; sAML, secondary acute myelogenous leukemia.
systemic chemotherapy.\textsuperscript{30-32} Although independent of treatment modality they are related to the age at which retinoblastoma is diagnosed. For children diagnosed in the first year of life the risk is 95%, for those diagnosed at 6 months of life the risk is 50%, and for those diagnosed at 1 year, the risk is 12%. New tumors are almost always (90%) anterior to the existing foci of tumor. New, peripheral tumors rarely (4%) develop following OAC. This means that fewer laser procedures are needed and there is less likelihood of laser damage to the iris and lens.\textsuperscript{31}

Recurrent intraocular disease: local recurrence of intraocular disease does develop in eyes treated with OAC.\textsuperscript{33} Interestingly it has been shown that retreatment with the same drugs via the same route results in local control in 83% of cases.\textsuperscript{34} The salvage rate is even higher in eyes without recurrent vitreous seeding. Eyes with recurrent vitreous seeding are now managed with the addition of intravitreal chemotherapy with success in > 90% of cases.

\section*{Summary}

OAC has revolutionized the management of unilateral and bilateral retinoblastoma for naive and those who failed previous treatment. It has resulted in saving more lives, many more eyes, considerably more vision and this has been accomplished even if the eye is blind with retinal detachment at diagnosis. It does not impair the immune system so children do not require PCP prophylaxis and they can receive all normal vaccinations on time. Unlike systemic chemotherapy, it does not slow growth and it has none of the radiation-related second cancers in eye retaining therapies. New, peripheral tumors rarely develop following OAC-unlike all other treatment options.

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\section*{References}

1. Abramson DH, Dunkel IJ, Brodie SE, et al. A phase I/II study of direct intraarterial (ophthalmic artery) chemotherapy with melphalan for intraocular retinoblastoma initial results. \textit{Ophthalmology}. 2008;115:1398.e1–1404.e1.
2. Abramson DH. Chemosurgery for retinoblastoma: what we know after 5 years. \textit{Arch Ophthalmol}. 2011;129:1492–1494.
3. Gobin YP, Dunkel IJ, Marr BP, et al. Intra-arterial chemotherapy for the management of retinoblastoma: four-year experience. \textit{Arch Ophthalmol}. 2011;129:732–737.
4. Suzuki S, Yamane T, Mohri M, et al. Selective ophthalmic arterial injection therapy for intraocular retinoblastoma: the long-term prognosis. \textit{Ophthalmology}. 2011;118:2081–2087.

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5. Klufas MA, Gobin YP, Marr B, et al. Intra-arterial chemotherapy as a treatment for intraocular retinoblastoma: alternatives to direct ophthalmic artery catheterization. AJNR Am J Neuroradiol. 2012;33:1608–1614.
6. Francis JH, Gobin YP, Dunkel IJ, et al. Carboplatin +/- topotecan ophthalmic artery chemosurgery for intraocular retinoblastoma. PLoS ONE. 2013;8:e72441.
7. Funes S, Sampor C, Villasante F, et al. Feasibility and results of an intraarterial chemotherapy program for the conservative treatment of retinoblastoma in Argentina. Pediatr Blood Cancer. 2018;65:e27086.
8. Chantada GL, Dunkel IJ, Schaiquevich PS, et al. Twenty-year collaboration between North American and South American retinoblastoma programs. J Glob Oncol. 2016;2:347–352.
9. Abramson DH, Dunkel IJ, Brodie SE, et al. Superselective ophthalmic artery chemotherapy as primary treatment for retinoblastoma (chemosurgery). Ophthalmology. 2010;117:1623–1629.
10. Brodie SE, Pierre Gobin Y, Dunkel IJ, et al. Persistence of retinal function after selective ophthalmic artery chemotherapy infusion for retinoblastoma. Doc Ophthalmol. 2009;119:13–22.
11. Schaiquevich P, buitrago E, Taich P, et al. Pharmacokinetic analysis of melphalan after superselective ophthalmic artery infusion in preclinical models and retinoblastoma patients. Invest Ophthalmol Vis Sci. 2012;53:4205–4212.
12. Schaiquevich P, Carcaboso AM, Buitrago E, et al. Ocular pharmacology of topotecan and its activity in retinoblastoma. Retina. 2014;34:1719–1727.
13. Taich P, Ceciliano A, Buitrago E, et al. Clinical pharmacokinetics of intra-arterial melphalan and topotecan combination in patients with retinoblastoma. Ophthalmology. 2013;212:889–897.
14. Dunkel IJ, Shi W, Salvaggio K, et al. Risk factors for severe neutropenia following intra-arterial chemotherapy for intra-ocular retinoblastoma. PLoS ONE. 2014;9:e108692.
15. Abramson DH, Daniels AB, Marr BP, et al. Intra-arterial chemotherapy (ophthalmic artery chemosurgery) for group D retinoblastoma. PLoS ONE. 2016;11:e0146582.
16. Abramson DH, Dunkel IJ, Brodie SE, et al. Bilateral superselective ophthalmic artery chemotherapy for bilateral retinoblastoma: tandem therapy. Arch Ophthalmol. 2010;128:370–372.
17. Abramson DH, Marr BP, Dunkel IJ, et al. Intra-arterial chemotherapy for retinoblastoma in eyes with vitreous and/or subretinal seeding: 2-year results. Br J Ophthalmol. 2012;96:499–502.
18. Munier FL, Beck-Popovic M, Balmer A, et al. Occurrence of sectoral choroidal occlusive vasculopathy and retinal arteriolar embolization after superselective ophthalmic artery chemotherapy for advanced intraocular retinoblastoma. Retina. 2011;31:566–573.
19. Abramson DH, Gobin YP, Dunkel I, et al. Highlighting complications over successes in occurrence of sectoral choroidal occlusive vasculopathy. Retina. 2011;31:1746; author reply 1747–1748.
20. Francis JH, Roosipu N, Levin AM, et al. Current treatment of bilateral retinoblastoma: the impact of intraarterial and intravitreous chemotherapy. Neoplasia. 2018;20:757–763.
21. Gobin YP, Marr BP, Dunkel IJ, et al. Retinoblastoma. J Neurosurg. 2012;116:470–472; author reply 471–472.
22. Abramson DH, Shields CL, Jabbour P, et al. Metastatic deaths in retinoblastoma patients treated with intraarterial chemotherapy (ophthalmic artery chemosurgery) worldwide. Int J Retina Vitreous. 2017;3:40–43.
23. Abramson DH, Shields CL, Munier FL, et al. Treatment of retinoblastoma in 2015: agreement and disagreement. JAMA Ophthalmol. 2015;133:1–7.
24. Wong JR, Morton LM, Tucker MA, et al. Risk of subsequent malignant neoplasms in long-term hereditary retinoblastoma survivors after chemotherapy and radiotherapy. J Clin Oncol. 2014;32:3284–3290.

25. Habib LA, Francis JH, Fabius AW, et al. Second primary malignancies in retinoblastoma patients treated with intra-arterial chemotherapy: the first 10 years. Br J Ophthalmol. 2017;102:272–275.

26. Fischer C, Petriccione M, Vitolano S, et al. The effect of ophthalmic artery chemosurgery on immune function in retinoblastoma patients: a single institution retrospective analysis. J Pediatr Hematol Oncol. 2017;39:555–559.

27. Akella SS, Francis JH, Knezevic A, et al. Growth patterns of survivors of retinoblastoma treated with ophthalmic artery chemosurgery. PLoS ONE. 2018;13:e0197052.

28. Rowlands MA, Mondesire-Crump I, Levin A, et al. Total retinal detachments due to retinoblastoma: outcomes following intra-arterial chemotherapy/ophthalmic artery chemosurgery. PLoS ONE. 2018;13:e0195395.

29. Abramson DH, Folberg R, Francis JH. Clinicopathologic correlation of choroidal invasion in retinoblastoma. Ophthalmology. 2018;125:568.

30. Wilson MW, Haik BG, Billups CA, et al. Incidence of new tumor formation in patients with hereditary retinoblastoma treated with primary systemic chemotherapy: is there a preventive effect? Ophthalmology. 2007;114:2077–2082.

31. Abramson DH, Francis JH, Dunkel IJ, et al. Ophthalmic artery chemosurgery for retinoblastoma prevents new intraocular tumors. Ophthalmology. 2012;120:560–565.

32. Lee TC, Hayashi NI, Dunkel IJ, et al. New retinoblastoma tumor formation in children initially treated with systemic carboplatin. Ophthalmology. 2003;110:1989–1994; discussion 1994–1995.

33. Francis JH, Levin AM, Zabor EC, et al. Ten-year experience with ophthalmic artery chemosurgery: ocular and recurrence-free survival. PLoS ONE. 2018;13:e0197081.

34. Francis JH, Abramson DH, Gobin YP, et al. Efficacy and toxicity of second-course ophthalmic artery chemosurgery for retinoblastoma. Ophthalmology. 2015;122:1016–1022.