

Original Investigation | CLINICAL SCIENCES

Intravitreal Melphalan for Persistent or Recurrent Retinoblastoma Vitreous Seeds

Preliminary Results

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IMPORTANCE Recurrent or persistent vitreous seeds following treatment of retinoblastoma poses difficult management and often leads to enucleation.

OBJECTIVE To describe the technique and evaluate the efficacy and complications of intravitreal melphalan for vitreous seeding from retinoblastoma.

DESIGN, SETTING, AND PARTICIPANTS This retrospective noncomparative analysis was conducted at a tertiary referral center. The study included 11 consecutive eyes of 11 patients with viable persistent or recurrent vitreous seeds following treatment of retinoblastoma.

INTERVENTIONS All eyes received intravitreal melphalan injection (20-30 µg) by transconjunctival pars plana route with concomitant triple-freeze cryotherapy at the injection site during needle withdrawal for prevention of extraocular seeding. Each patient was offered planned 6 monthly cycles.

MAIN OUTCOMES AND MEASURES Vitreous seed control and complications of therapy.

RESULTS The mean patient age at vitreous injection was 37 months (median, 27 months; range, 16-82 months). Viable vitreous seeds involved 2 (n = 1), 3 (n = 4), or 4 (n = 6) quadrants. The solid intraretinal retinoblastoma and subretinal seeds showed regression in all eyes following intravenous chemotherapy (n = 6) or intra-arterial chemotherapy (n = 5). There were a total of 55 injections, with a mean number per patient of 5 (median, 6; range, 2-6). Fewer than 6 injections (n = 5) were delivered owing to complete vitreous seed control and parental desire to avoid more injections. By a mean of 9 months' follow-up (median, 9 months; range, 6-16 months), therapeutic success with complete vitreous seed regression was achieved in all 11 cases (100%). Globe salvage was attained in all cases (100%). Further vitreous seed development did not occur in any case. Complications included focal retinal pigment epithelial mottling near the site of chemotherapy injection (2 eyes) and nonaxial posterior lens opacity (2 eyes). There was no case of extraocular tumor extension, hypotony, or phthisis bulbi.

CONCLUSIONS AND RELEVANCE These preliminary short-term results suggest that intravitreal melphalan injection for persistent or recurrent vitreous retinoblastoma seeding can provide tumor control with minimal toxicity and complications.

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Intravenous chemotherapy (IVC) and intra-arterial chemotherapy (IAC) have improved tumor control in patients with retinoblastoma over the past 2 decades, allowing for dramatic tumor reduction with salvage of the globe, often in an eye that otherwise would have been managed with enucleation.¹⁻⁶ Furthermore, there is often some degree of visual acuity retained or regained.^{7,8} However, the most challenging aspect of retinoblastoma therapy is control of subretinal or vitreous seeds.^{9,10} In general, solid tumors show predictably excellent response to both methods. Subretinal tumor seeds show partial or complete response to either method. Vitreous seeds are the least responsive to IVC or IAC, partly owing to their location in the vitreous remote from blood supply.

In recent years, the role of intravitreal chemotherapy has been explored for control of vitreous seeding from retinoblastoma.⁶ In 2003, Kaneko and Suzuki¹¹ evaluated 8 $\mu\text{g}/0.1$ mL and later 20 to 30 $\mu\text{g}/0.1$ mL of intravitreal melphalan, acknowledging improved control using the latter. Munier and associates^{12,13} reported minimal toxicity and complication with the 20- to 30- $\mu\text{g}/0.1$ mL dose of intravitreal chemotherapy using melphalan in 23 consecutive eyes. They observed control of vitreous seeds in 87% of cases. More recently, Ghassemi and Shields¹⁴ reported improved control with a higher dose of melphalan and defined the limits of intravitreal melphalan as the low dose of 8 $\mu\text{g}/0.1$ mL, which provided 43% tumor control, while the high dose control of 50 $\mu\text{g}/0.1$ mL provided 100% control, but with risks for hypotony and/or phthisis bulbi. They suggested the intermediate dose of a 20 to 30 $\mu\text{g}/0.1$ mL for tumor control with minimal complication. In this report, we specifically evaluated the efficacy, toxicity, and complications of 20- to 30- $\mu\text{g}/0.1$ mL dose of intravitreal chemotherapy using melphalan in a consecutive series of patients.

Methods

Institutional review board approval from Wills Eye Hospital was obtained for this retrospective analysis. Inclusion criteria were eyes with viable vitreous retinoblastoma seeds that were persistent or recurrent following standard treatment methods, in which the remainder of the eye was stable, and enucleation was the only other option. Eyes that qualified for inclusion were prescribed intravitreal melphalan between January 2011 and June 2013 and had at least 6 months of follow-up from the date of first injection. Exclusion criteria were eyes that displayed additional viable solid intraretinal retinoblastoma or viable subretinal seeds or those deemed at risk for metastatic disease with uveal or optic nerve invasion. Written informed parental consent was obtained and risks for extraocular extension, vitreous hemorrhage, retinal detachment, and intraocular infection were explained. These cases have not been previously published in any series.

The patients were examined under anesthesia, and intraocular pressure, external inspection, anterior segment assessment, and indirect ophthalmoscopy were performed. Documentation was provided with anterior segment drawings, large fundus drawings, anterior segment and fundus photography,

anterior segment and fundus fluorescein angiography, ultrasonography, and anterior and posterior segment optical coherence tomography.

Data were collected regarding demographic details of patients including age at presentation, age at vitreous melphalan injection, race/ethnicity, and sex. Data regarding tumor features were collected at the time of initial presentation including retinoblastoma stage (International Classification of Retinoblastoma), largest tumor size in basal dimension (millimeter [mm]) and thickness (mm), and initial treatment method. Data regarding tumor features at the time of vitreous melphalan injection included the status of the main (solid) retinoblastomas, the status of subretinal seeds and of vitreous seeds (regressed, persistent, or recurrent), the location of vitreous seeds with regard to quadrant, the anteroposterior site, and the number of clock hours involved.

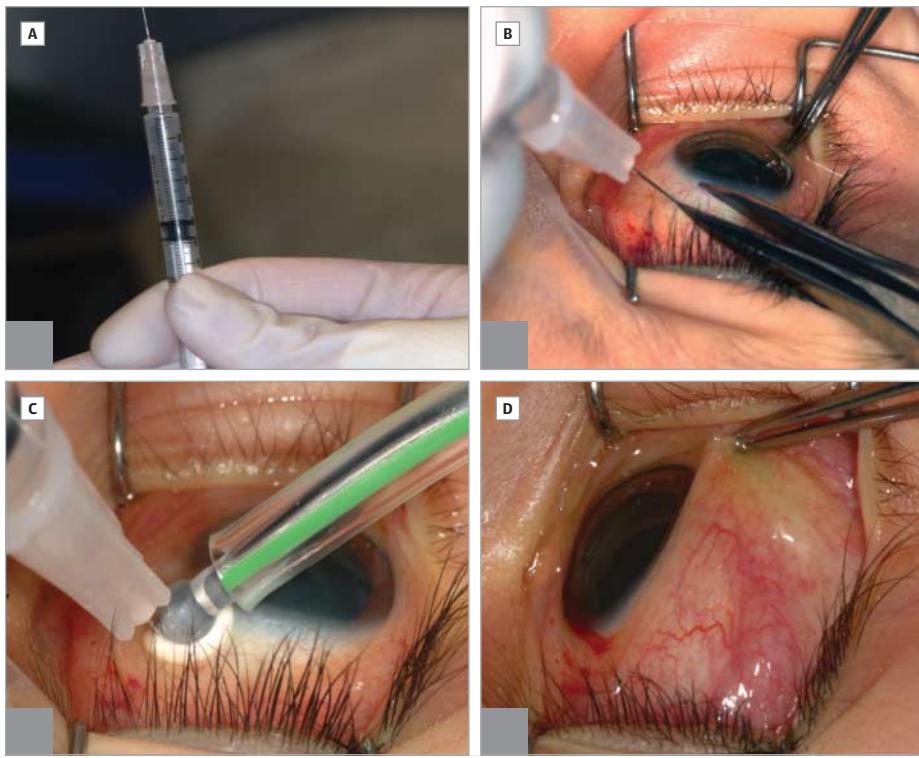
The melphalan injection was performed under general anesthesia using a sterile technique including draping of the involved eye. The medication was obtained immediately after preparation from the Thomas Jefferson University Pharmacy, Philadelphia, Pennsylvania, as a 0.5-mL clear solution with concentration of 20 $\mu\text{g}/0.1$ mL melphalan. Owing to the short half-life activity of melphalan of approximately 90 minutes, time efficiency in delivery and injection of medication was considered. Following delivery to the operating room, the medication was transferred to a sterile 1-mL syringe and a 31-gauge needle was attached (**Figure 1**). Vitreous injection was performed through the pars plana, approximately 2.75 to 3.0 mm from the limbus, depending on patient age. The clock hour of injection was selected based on vitreous seed activity, with the goal to inject 1 to 2 clock-hours' distance from the vitreous seeds to avoid direct contact with the seeds and avoid extraocular extension. After medication injection, while the needle was still in the eye, cryotherapy was applied to the injection site to include the needle in the ice ball. The needle was withdrawn through the ice ball during the first freeze. Triple-freeze-thaw cryotherapy was completed. The eyeball was gently moved with forceps back and forth to cause drug dispersion throughout the vitreous cavity and preferably to the site of vitreous seeds. Following injection, indirect ophthalmoscopy was performed for inspection of vitreous or retinal complications. Topical corticosteroid/antibiotic ointment was applied. The eye was unpatched and without further postoperative medications.

Patients were examined monthly during the intravitreal melphalan injections. After completion of the treatment, follow-up was extended based on globe response. Outcome measures included vitreous seed control, treatment complications, and medication toxicity. Therapeutic success was defined as complete regression of all vitreous seeds without recurrence. Therapeutic failure was defined as persistence or recurrence of viable vitreous seeds.

Results

Of 18 eyes managed with intravitreal injection of melphalan for viable vitreous seeding, 11 eyes of 11 patients were in-

Figure 1. Intravitreal Melphalan Injection Technique



A, Reconstituted melphalan in a 1-mL sterile syringe with a 31-gauge needle. B, Injection is made through the pars plana, approximately 3 mm from the limbus, depending on patient age. C, At withdrawal of the needle from the eye, cryotherapy is performed with the triple-freeze-thaw technique and creates an ice ball through which the needle is withdrawn. D, The eyeball is gently jiggled to disperse the chemotherapy throughout the gelatinous vitreous.

cluded in this study. The 7 nonincluded eyes did not reach criteria of chemotherapy dosage of 20 to 30 $\mu\text{g}/0.1\text{ cc}$ ($n = 2$) or minimum follow-up of 6 months ($n = 5$). The demographic details are summarized in Table 1.

At the time of initial presentation, the affected eye was classified (International Classification of Retinoblastoma) as group C ($n = 1$; 9%), group D ($n = 9$; 82%), or group E ($n = 1$; 9%) (Table 2). The mean basal tumor diameter was 13 mm (median, 12.5 mm; range, 6-22 mm) and the mean thickness was 8 mm (median, 8; range, 3-13 mm). Primary treatment included intravenous vincristine, etoposide, and carboplatin for 6 cycles ($n = 6$; 55%) or IAC ($n = 5$; 45%) using combination melphalan and topotecan. In 6 cases, secondary treatment was necessary for tumor or seed control, as listed in Table 2. These therapies led to solid retinoblastoma control in all cases ($n = 11$; 100%) and subretinal seed control in all 7 eyes with subretinal seeds (100%). However, all 11 eyes showed viable vitreous seeds, classified as persistent ($n = 3$; 27%) or recurrent ($n = 8$; 73%).

At the time of vitreous seeding, the mean patient age at injection was 37 months (median, 27 months; range, 16-82 months). The vitreous seeds involved 2 ($n = 1$; 9%), 3 ($n = 4$; 36%), or 4 ($n = 6$; 54%) quadrants of the vitreous gel. Intravitreal melphalan injection of a 20- to 30- $\mu\text{g}/0.1\text{ mL}$ dose for a proposed 6 cycles was delivered (Figure 2). A total of 55 injections was administered in 11 eyes, with a mean of 5 sessions (median, 6; range, 2-6) at a median interval of 1 month. Fewer than 6 injections were given in cases in which complete vitreous seed control was achieved and the family requested no further treatment ($n = 4$). Following injection, cryotherapy

(triple freeze thaw) was applied in every case. There was no aspiration of aqueous or vitreous liquid. Gentle ocular jiggling to disperse chemotherapy was applied for 3 minutes in each case.

On follow-up, complete vitreous seed resolution was found following a mean of 2 injections (median, 3; range, 1-6). Following chemotherapy injections, all vitreous seeds remained regressed, with no evidence of vitreous seed recurrence by mean follow-up of 9 months (median, 9 months; range, 6-16 months). Of those 6 patients followed up for 9 months or longer (mean, 12 months) from first injection, there was no vitreous seed recurrence.

There were no complications of vitreous hemorrhage, vitreous infection, retinal hemorrhage, or retinal detachment in any case. There was no conjunctival fibrosis or erythema at the site of injection, and there was no case of extrascleral tumor extension, hypotony, or phthisis bulbi. Minor focal retinal pigment epithelial mottling of 5-mm diameter at the ora serrata along the meridian of the chemotherapy injection site was noted in 2 eyes and extra-axial posterior lens opacity in 2 eyes. Fluorescein angiography in each case showed no sign of retinal vasculopathy or retinal edema.

Discussion

Intravenous chemotherapy (chemoreduction) and IAC are currently the 2 most commonly used globe-conserving therapies for retinoblastoma.¹ Based on the International Classification of Retinoblastoma, globe salvage (IVC vs IAC) is

Table 1. Demographics of 11 Patients Who Received Intravitreal Melphalan for Vitreous Retinoblastoma Seeds

Features at the Time of Vitreous Injection	No. (%) (n = 11)
Age, mean, mo	37
Median (range)	27 (16-82)
Race/ethnicity	
White	8 (73)
African American	2 (18)
Hispanic	1 (9)
Sex	
Male	6 (55)
Female	5 (45)
Heredity	
Sporadic	10 (91)
Familial	1 (9)
Genetics	
Somatic	5 (45)
Germline	6 (55)
Laterality of retinoblastoma	
Unilateral	5 (45)
Bilateral	6 (55)
Eye with active vitreous seeds	
Right	6 (55)
Left	5 (45)

impressive for group B (100% vs IAC not used for group B), group C (94% vs 100%), and group D (47% vs 100%).^{10,15} Group A eyes are generally not treated with methods of chemotherapy because they are sufficiently controlled with nonchemotherapy methods. On the other end of the spectrum, group E eyes are usually managed with enucleation owing to advanced disease, lack of visible healthy retina, anticipated poor or no visual outcome, and 24% to 50% risk for high-risk retinoblastoma at risk for metastasis.¹⁶⁻¹⁹ In those cases in which both eyes show advanced retinoblastoma with groups D and/or E, IVC, plus IAC, has been successful in globe salvage in 65%, often with limited visual acuity.¹⁶

Vitreous seeds pose a special problem in retinoblastoma management because they are remote from the blood supply and rely on diffusion of chemotherapy into the vitreous gel from the retina. Lack of vitreous seed control is often the limiting factor in globe salvage following chemotherapy or radiotherapy. In 2002, an analysis of 158 eyes with retinoblastoma found 54 with active vitreous seeds at presentation.⁹ Of those, following standard IVC, vitreous seed recurrence was found in 50% by 5-year follow-up, generally leading to plaque radiotherapy, external beam radiotherapy, or enucleation for ultimate control.⁹ In 2011, an analysis of 17 eyes with retinoblastoma and managed with IAC, of which 9 had vitreous seeding at presentation, vitreous seed control was observed in 6 (67%) and persistence/recurrence in 3 (33%).¹⁰ These observations indicated that control of vitreous seeding can be challenging with both IVC and IAC.

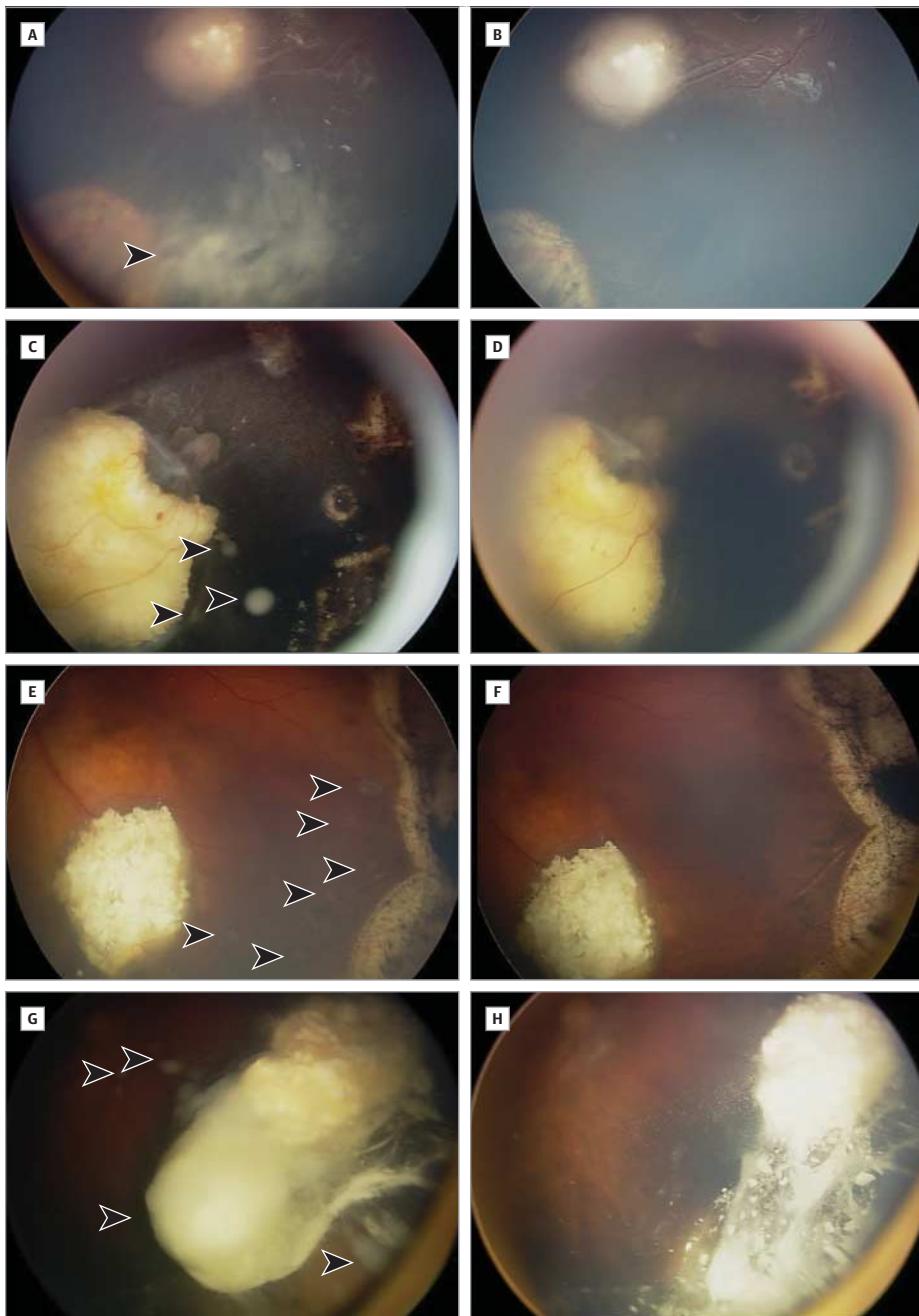
Table 2. Treatment Summary of 11 Patients Who Received Intravitreal Melphalan for Vitreous Retinoblastoma Seeds

Case No.	Findings at Initial Examination			Outcome of Previous Therapy			Vitreous Seed Features		Intravitreal Melphalan Therapy		Vitreous Seed Outcome	
	ICRB Group	Primary Treatment	Secondary Treatment	Solid Tumor	Subretinal Seeds	Vitreous Seeds	Quadrants With Vitreous Seeds, No.	Vitreous Seed Location (Anterior-posterior)	Melphalan Dose, µg/0.1 mL (No. of Injections)	No. of Injections/mo	Vitreous Seed Response (Follow-up, mo)	Complications
1	D	VEC × 6	IAC × 3, IVitMtx	Regress	Regress	Persist	4	Diffuse	30 (2) 20 (4)	6	Regress (16)	None
2	D	IAC × 3	None	Regress	Regress	Persist	3	Diffuse	30 (6)	6	Regress (6)	None
3	E	IAC × 4	None	Regress	NA	Recur	2	Anterior	20 (3) 30 (3)	6	Regress (9)	None
4	D	IAC × 3	Plaque	Regress	Regress	Recur	3	Anterior	20 (4)	4	Regress (7)	None
5	D	VEC × 6	PBRT, IAC × 3	Regress	NA	Recur	4	Diffuse	20 (1) 30 (5)	6	Regress (6)	None
6	D	VEC × 6	IAC × 4	Regress	Regress	Recur	4	Posterior	20 (4)	4	Regress (12)	None
7	D	VEC × 6	None	Regress	NA	Persist	3	Posterior	20 (4) 30 (2)	6	Regress (12)	RPE mottling
8	C	IAC × 6	None	Regress	Regress	Recur	4	Posterior	20 (3)	3	Regress (12)	None
9	D	IAC × 4	None	Regress	NA	Persist	4	Diffuse	30 (6)	6	Regress (6)	RPE mottling Peripheral lens opacity
10	D	VEC × 6	Plaque, IAC × 5	Regress	Regress	Recur	3	Posterior	20 (2)	2	Regress (9)	None
11	D	VEC × 6	IAC × 4	Regress	Regress	Recur	4	Diffuse	30 (6)	6	Regress (6)	Peripheral lens opacity

Abbreviations: IAC, intra-arterial chemotherapy; ICRB, International Classification of Retinoblastoma; IVitMtx, Intravitreal methotrexate; NA, not applicable; PBRT, proton-beam radiotherapy; Persist, persistent; Plaque, plaque

radiotherapy; Recur, recurrent; Regress, regression; RPE, retinal pigment epithelium; VEC, vincristine, etoposide, carboplatin (intravenous).

Figure 2. Intravitreal Melphalan Controls Vitreous Seeding From Retinoblastoma



In case 1, there were viable persistent vitreous seeds following chemoreduction for bilateral retinoblastoma and intra-arterial chemotherapy for persistent vitreous seeds in the right eye (OD). Before (A) and after (B) intravitreal melphalan (6 injections), OD demonstrated complete regression of all seeds at 7 months' follow-up and with no complication. Control continues at 16 months' follow-up. In case 5, there were viable recurrent vitreous seeds following chemoreduction for bilateral retinoblastoma and proton-beam radiotherapy (elsewhere) for persistent vitreous seeds (OD). The left eye (OS) had been enucleated for advanced retinoblastoma (elsewhere). Before (C) and after (D) intravitreal melphalan (6 injections), OD demonstrated complete regression of all seeds at 6 months' follow-up and with no complication. In case 8, there were subtle, viable recurrent vitreous seeds near the ora serrata for 12 clock hours following intra-arterial chemotherapy for unilateral retinoblastoma (OS). Before (E) and after (F) intravitreal melphalan (3 injections) demonstrated complete regression of all seeds at 12 months' follow-up and with no complication. In case 9, there were obvious, viable persistent vitreous seeds overlying calcified regressed retinoblastoma near the ora serrata following intra-arterial chemotherapy for unilateral retinoblastoma (OD). Before (G) and after (H) intravitreal melphalan (6 injections) demonstrated complete regression of all seeds at 6 months' follow-up. The patient developed asymptomatic nonaxial posterior lens opacity.

Vitreous injection of chemotherapy has been previously attempted with variable success using thiotepa or methotrexate.²⁰⁻²² More recently, intravitreal melphalan has been found safe and remarkably effective for control of vitreous seeds.¹¹⁻¹⁴ Munier and colleagues^{12,13} noted regression of vitreous seeds in 87% of eyes treated with intravitreal melphalan. Ghassemi and Shields¹⁴ subsequently evaluated the limits of melphalan injection, commenting on reduced vitreous seed control with 8 $\mu\text{g}/0.1$ cc and excellent control with a higher dose of 50 $\mu\text{g}/0.1$ cc but limited by chronic hypotony. In this report, we specifically investigated tumor control and complications with an intermediate dose of 20 to 30 $\mu\text{g}/0.1$ cc.

It should be emphasized that all eyes in this series had received previous standard IVC and/or IAC. All eyes had viable vitreous seeding. Each eye was treated with intravitreal melphalan at an intermediate dose for a planned 6 monthly injections. We found complete control relatively early in the course of therapy, usually after the second injection. Despite early control, we preferred to follow the protocol of 6 monthly injections. There was therapeutic success with vitreous seed regression in all 11 eyes (100%). The globe was saved in all cases. There was no case of extraocular tumor extension, hypotony, or phthisis bulbi. However, it should be noted that we used precautionary cryotherapy at the site of injection during needle withdrawal.

There is concern for needle injection or aspiration in an eye with retinoblastoma because this tumor is friable and could potentially seed through the tract into the subconjunctival or orbital space.²³ We had no tumor dissemination in our series of 55 injections because we were careful to inject chemotherapy near, but not immediately at, the site of seeding to avoid adherence of seeds to the needle tip. Extraocular extension of retinoblastoma classically appears as a gelatinous, vascular mass, typically under the conjunctiva and was not found in any of our cases. Similar results were achieved by Munier and associates,¹² with no extraocular tumor spread following 122 injections. In fact, they subtitled their report “From Prohibition to Conditional Indications” to emphasize that injection could be an acceptable strategy for certain patients. Likewise, in our previous report of 33 injections in 12 eyes, we found no case of extraocular extension.¹⁴

In addition to using intravitreal chemotherapy as a sole treatment for persistent or recurrent vitreous seeds, there has been interest in using this route in combination with IVC, IAC, or subtenon chemotherapy. In 2012, Smith and colleagues²⁴ reported on the combined use of intravitreal carboplatin and subconjunctival carboplatin for vitreous seeds from retinoblastoma in 2 patients. Both eyes came to enucleation, and histopathology showed the scleral needle tract to be closed and without tumor. In each case, 3-year follow-up disclosed no extracocular extension.

The role of intravitreal chemotherapy at the time of vitrectomy in eyes with treated retinoblastoma continues to be of interest. In a rabbit model, Shimoda and associates²⁵ perfused various concentrations of melphalan into the vitreous during pars plana vitrectomy. They found that a 5- μ g/mL per-

fusion dose was nontoxic to the retina, whereas 10- μ g/mL and 20- μ g/mL doses showed histopathologic toxicity with inner retinal necrosis. In 2009, Ohshima and colleagues²⁶ reported on a single case of retinoblastoma that was managed with IAC and then intravitreal melphalan for vitreous seeds but ultimately underwent vitreous surgery with melphalan perfusion of 5- μ g/mL concentration with no extraocular extension at 12 months' follow-up.

There were limitations to our study that should be identified. First, intravitreal melphalan was studied for its effect on vitreous seeds only and not subretinal seeds or solid intraretinal tumor. Our results cannot be extrapolated to those other sites. Second, this cohort, with minimum 6 months' (median, 9 months) follow-up, should be followed up for a longer period to ascertain the long-term stability of our results. Lastly, there could be unforeseen long-term complications of this approach, so caution with its use is advised.

Conclusions

In summary, our preliminary short-term results found intravitreal melphalan to be effective for control of vitreous seeding from retinoblastoma and with minimal complications. We caution against the overuse of this technique because there could be risks for extraocular extension of seeds and toxicity to the retina. We suggest that this method continue to be cautiously investigated at experienced retinoblastoma centers and data gathered for more comprehensive and long-term understanding of the role of intravitreal chemotherapy for this serious ocular malignancy of childhood.

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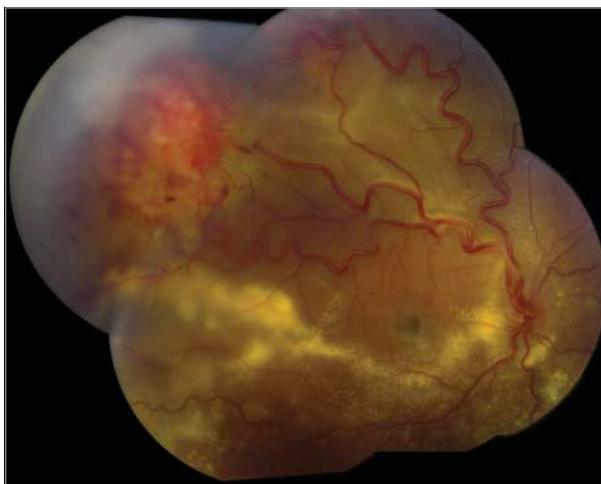
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OPHTHALMIC IMAGES

Retinal Hemangioblastoma

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A 12-year-old girl presented with exotropia of the right eye. Her visual acuity was counting fingers in the right eye with an afferent pupillary defect. The results of an examination of her left eye were normal. Fundoscopy revealed a large hemangioblastoma with a shallow serous detachment of the macula. Fortunately, genetic workup for von Hippel-Lindau disease was negative.