

INTRAVITREAL CHEMOTHERAPY FOR VITREOUS SEEDING CAUSED BY RETINOBLASTOMA

Intravitreal and intraarterial administration of chemotherapy are important and effective methods of treatment, but they must be used with caution.

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Vitreous seeding is one of the primary reasons for treatment failure following conservative management of retinoblastoma.^{1,2} In our hands, until

early 2006, most children with recurrent vitreous seeding were managed with plaque radiotherapy, external beam radiotherapy, or enucleation.^{1,2} In 2006, following the initial experience of Kaneko and Suzuki in Japan,³ we performed the first intravitreal injection of melphalan for the management of retinoblastoma vitreous seeds in the United States.⁴ Quite cautiously, we sequentially injected the affected eyes of three patients with previously treated retinoblastoma and extensive recurrent vitreous seeding. Our initial experience was that all three cases showed dramatic response with rapid seed regression. However, due to the low chemotherapy dose (8 µg/0.1 cc melphalan) used at that time, seed recurrence was a problem.

Since then, melphalan dose escalation to between 20 µg/0.1 cc and 30 µg/0.1 cc has allowed reliably improved results, with vitreous seed control in nearly every case.^{5,6} Today, vitreous seeds no longer readily necessitate enucleation, as these cases can be managed safely and reliably with intravitreal chemotherapy (IVitC).⁴⁻⁶ In 2012, Ghassemi and Shields⁴ and Munier et al⁷ each reported on the safety and efficacy of IVitC for vitreous seeds. Munier et al noted that IVitC was no longer prohibited for retinoblastoma management.⁷ This approach has now been adopted at almost all major retinoblastoma centers worldwide.

In this article we describe a child with retinoblastoma treated initially with intraarterial chemotherapy (IAC) and then subsequently with intravitreal melphalan for recurrent vitreous seeding.

CASE REPORT

A 26-month-old male initially presented for evaluation of a lazy eye with leukocoria and was found to have retinoblastoma. The patient was referred to Wills Eye Hospital Ocular Oncology Service for an opinion.

On examination, visual acuity was fix and follow in the right eye (OD), and no fix or follow in the left eye (OS). Intraocular pressures were normal in both eyes. OD was healthy, but OS showed obvious leukocoria (Figure 1). On funduscopy, there was total retinal detachment up against the back of the lens, with exophytic retinoblastoma classified as group D and measuring 16.0 mm in basal dimension and 10.6 mm in thickness (Figure 2A). Both vitreous and subretinal seeds were noted. Ultrasonography and magnetic resonance imaging using T1- and T2-weighted scans showed



AT A GLANCE

- Vitreous seeding is an important cause of treatment failure following conservative management of retinoblastoma.
- Intravitreal chemotherapy (IVitC) and intraarterial chemotherapy are effective approaches to managing patients with retinoblastoma and should be selected based on clinical examination, previous treatments, and tumor manifestations.
- The main indications for IVitC include patients with vitreous seeds unresponsive to standard therapy or recurrent vitreous seeds after previous standard therapy.



Figure 1. External image shows prominent leukocoria OS in a 26-month-old male with retinoblastoma.

no evidence of extrascleral or optic nerve extension. The patient was diagnosed with unilateral sporadic (group D) retinoblastoma OS. After discussion of therapies, treatment with two-agent IAC using melphalan and topotecan was planned.

The patient received three cycles of IAC using melphalan 5 mg/30 cc and topotecan 1 mg/30 cc delivered through the left ophthalmic artery to the OS. The tumor showed initial dramatic response (Figure 2B), but recurrent vitreous

seeding (Figure 2C) overlying the calcified, regressed main tumor necessitated IVitC with melphalan 20 µg/0.1 cc and topotecan 20 µg/0.1 cc.

After six cycles of IVitC delivered on a weekly basis, complete regression of vitreous seeds and stable regressed retinoblastoma were seen OS (Figure 2D). Side effects from the intravitreal injections included minor posterior synechiae and localized iris pigment epithelial atrophy near the injection site. The crystalline lens was clear. The main tumor and all vitreous seeds were regressed at last examination.

DISCUSSION

Over the past decade, IAC has emerged as a powerful treatment for retinoblastoma, especially in patients with unilateral disease.¹ The technique of IAC involves precise delivery of a small dose of chemotherapy directly into the ophthalmic artery, thus minimizing exposure to systemic circulation and related potential toxic effects.⁸

Initially described in 2004 by Yamane and Kaneko⁹ in Japan, IAC was explored in the United States by teams in New York and Philadelphia as a method for salvaging advanced cases of retinoblastoma without the need for external beam radiotherapy or enucleation.^{1,2,10} At first, this therapy was employed for

eyes in which standard intravenous chemotherapy failed. Later, following documented success, this treatment was used as primary therapy.

Analysis revealed that success with IAC was achieved in 100% of group B eyes, 100% of group C eyes, 94% of group D eyes, and 36% of group E eyes.¹¹ It should be noted that IAC is not generally used for group A disease, as focal methods of laser photocoagulation or cryotherapy are typically sufficient.^{1,2} The technique of IAC requires skill and experience, as there is a relatively steep learning curve that affects treatment outcomes.

Despite treatment success, complications can include retinal vascular obstruction or temporary spasm, choroidal ischemia, optic nerve ischemia, vitreous hemorrhage, and other events.^{2,8,11} These effects are weighed in comparison with the potential loss of an eye and loss of life for patients with retinoblastoma. In the patient discussed above, the large tumor size, unilateral tumor, and non-germline mutation led us to use a conservative approach.

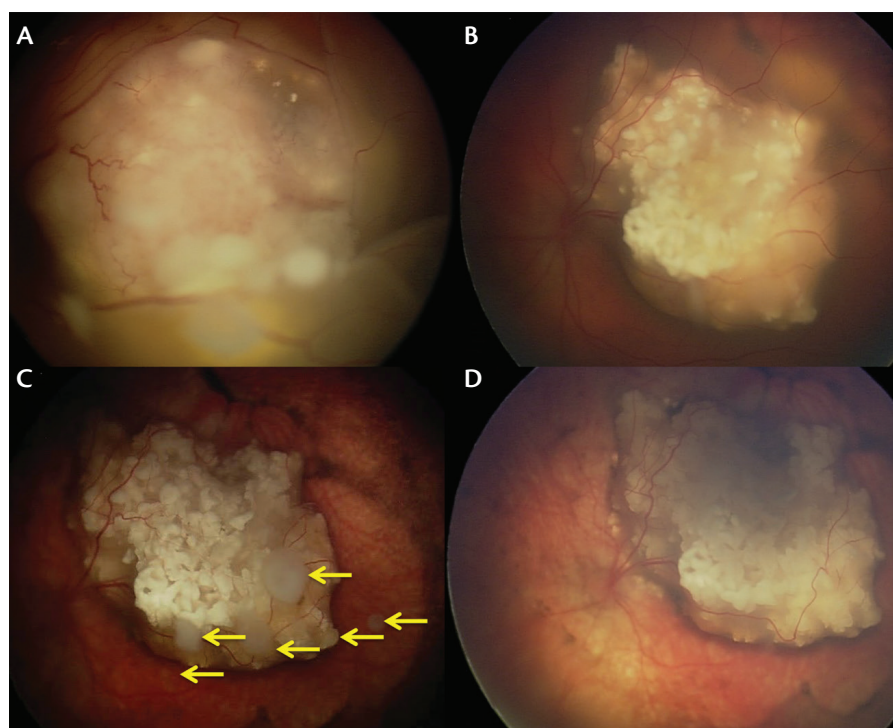


Figure 2. RetCam II (Clarity Medical Systems) imaging demonstrated viable retinoblastoma OS (A). The tumor showed substantial regression after three cycles of IAC (B), but recurrence was detected in the vitreous with seeds 5 months later (C). After eight cycles of IVitC treatment, the vitreous seeds were completely regressed, leaving a calcified regressed retinoblastoma scar (D).

“ IVitC with melphalan is a powerful approach to vitreous seed control, but it can lead to local toxic effects in both anterior and posterior segments of the eye.

After three treatments of IAC in our case, excellent solid tumor control was achieved, but vitreous seed recurrence was noted, necessitating IVitC with melphalan. The main indications for IVitC include vitreous seeds unresponsive to standard therapy and recurrent vitreous seeds after previous standard therapy.^{1,2} In the case discussed here, the patient demonstrated features of the latter group, with recurrent vitreous seeds despite three cycles of IAC treatment. Following these guidelines, our patient underwent IVitC treatments for vitreous seed control. As reported by Ghassemi and Shields, low-dose melphalan (8–10 µg/30 cc) demonstrates less control with minimal side effects, while higher-dose melphalan (30–50 µg/30 cc) shows excellent control but with possible serious side effects of hypotonia and phthisis bulbi as the dosing nears 50 µg.⁴ Thus, 20 µg/30 cc melphalan per cycle appears to be ideal.⁶

We advise caution when the technique of IVitC is used, as risks of extraocular extension of seeds from needle perforation and toxicity to the retina from chemotherapy can occur.^{5,12} In 2016, a study of 192 injections of IVitC with melphalan and/or topotecan revealed side effects including focal retinal pigment epithelial mottling at the site of the injection (32%), minor focal lens opacity not requiring cataract surgery (25%), transient focal vitreous hemorrhage (13%), transient hypotony (8%), transient retinal hemorrhage (5%), optic disc edema (3%), and hemorrhagic retinal necrosis (3%).⁶ Further review disclosed that each IVitC injection (30 µg/0.1 cc) resulted in a decrement of approximately 5% in retinal function as measured by electroretinography.¹³ Anterior segment abnormalities at or near the injection site were also noted in 7% of patients after IVitC with melphalan.¹⁴ Other anterior segment abnormalities included cataract, iris depigmentation or thinning, iris recession, conjunctival bleb, and focal scleromalacia.¹⁴ Thus, IVitC with melphalan is a powerful approach to vitreous seed control, but it can lead to local toxic effects in both anterior and posterior segments of the eye. Potential complications should be considered prior to administration.^{6,13,14}

CONCLUSION

IAC and IVitC are important routes of chemotherapy administration for patients with retinoblastoma. There are a variety of treatment types, and options should be chosen based on clinical examination, previous treatments, and tumor manifestations. Specific chemotherapies can be effective for retinoblastoma, but clinicians should understand the potential adverse effects. ■

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