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Pushing the limit: Globe salvage of Group D retinoblastoma with severe vitreous seeding with intra-arterial chemotherapy and 15 cycles of intravitreal chemotherapy

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ABSTRACT

Purpose: To report the successful treatment of persistent retinoblastoma vitreous seeding with 6 cycles of intra-arterial chemotherapy and 15 cycles of intravitreal chemotherapy injections.
Observations: A three-year-old female presented to the ocular oncology clinic with Group D retinoblastoma with severe vitreous seeding. The patient received 3 cycles of intra-arterial chemotherapy (melphalan, topotecan, and carboplatin) and 15 cycles of intravitreal chemotherapy (melphalan and combined melphalan/topotecan). Complete tumor regression and resolution of vitreous seeding was achieved. The best corrected visual acuity in the affected eye was 20/50.
Conclusions and Importance: Intravitreal chemotherapy for retinoblastoma vitreous seeding is often restricted to 8 treatment cycles. Patients who do not respond after 8 cycles face salvage therapy with radiation or enucleation. This is a case in which prolonged intravitreal chemotherapy delivery was well tolerated and resulted in sustained tumor remission, with useful visual acuity in the treated eye.

1. Introduction

Retinoblastoma, the most common childhood intraocular tumor, arises from the retina and may grow downwards towards the choroid or anteriorly toward the vitreous cavity.[1] The presence of vitreous seeding is a poor prognostic indicator.[2,3] Prior to targeted drug delivery, eyes with vitreous seeding were the least likely to be salvaged with radiation or intravenous chemotherapy.[4] The introduction of local therapy with intra-arterial and intravitreal melphalan increased local drug delivery and revolutionized the treatment of eyes with vitreous seeding, greatly increasing eye salvage rates.[5–7]

To date, there have been no large clinical trials to determine intravitreal chemotherapy delivery protocols. Most clinical guidance is based on historical data from retrospective studies and case series. Kaneko and Suzuki et al. isolated melphalan as an effective in-vitro therapy in 1987.[8] They later utilized rabbit models to titrate melphalan intravitreal concentration to a therapeutic threshold that avoided excessive retinal toxicity.[9] Extrapolation of their results to the volume of the human vitreous cavity yielded a dose of 20–30μg, a range still widely accepted as the standard dose for intravitreal melphalan. In 2012, Munier et al. popularized the use of intravitreal melphalan after publishing detailed protocols that prevented the spread of tumor from injection delivery. Injections were given in one-week intervals and treatment was limited to 8 intravitreal injections per eye.[7] The authors did not specify why a limit of 8 cycles was selected. However, in the absence of any guiding clinical trials, a treatment cap of approximately 8 injections was carried forward by future investigators.

Persistent vitreous seeding after intra-arterial and intravitreal chemotherapy is deemed a treatment failure, leading to enucleation, or less commonly, salvage therapy with external beam radiation. The utility of intravitreal chemotherapy for recalcitrant vitreous seeding beyond 8 injection cycles is sparsely documented. Prolonged intravitreal chemotherapy delivery may potentially lead to higher rates of globe salvage and avoid the need for salvage therapies and their associated morbidity. We share our experience with a patient who received 15 cycles of intravitreal chemotherapy for the treatment of persistent vitreous seeding with good visual outcome and limited drug toxicity.

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2. Case report

A three-year-old female presented to ocular oncology clinic for evaluation after her mother noted a floating white spot in the pupil of her left eye. Visual acuity at presentation was 20/50 in both eyes by LEA vision testing. Initial fundoscopic examination was normal in the right eye. In the left eye, a superotemporal white retinal mass with overlying vitreous seeding was noted. Initial examination under anesthesia (EUA) confirmed a white, endophytic retinal tumor with dense vitreous seeding extending from the tumor apex to the posterior lens capsule (Fig. 1 [A] & [B]). B-scan ultrasonography showed intra-lesion calcification (Fig. 1 [C]). Magnetic resonance imaging (MRI) of the brain and orbit with and without contrast showed no evidence of optic nerve enhancement and no extraocular or central nervous system involvement. A diagnosis of Group D retinoblastoma (by the International Classification for Intraocular Retinoblastoma system) was made. Peripheral blood submitted for germline genetic testing (Invitae Genetics, San Francisco, CA) revealed no pathogenic mutations, variants of unknown significance, deletions, or duplications in the RB1 gene.

One week after the initial EUA, intra-arterial chemotherapy (IAC) treatment with melphalan was administered. Follow-up EUA performed one month after treatment showed diminished tumor size with persistent vitreous seeding. The patient received 3 cycles of intra-arterial melphalan, followed by 3 cycles of intra-arterial triple therapy (melphalan, topotecan, and carboplatin) due to persistence of vitreous seeding. IAC cycles were spaced one month apart and were delivered in the first 6 months following presentation. Focal consolidation with four rounds of cryotherapy to the primary tumor site was given approximately two weeks apart in the initial two months after presentation. Intravitreal chemotherapy was initiated 17 days after initial IAC treatment. The patient received a total of 15 cycles of intravitreal chemotherapy over a 5-month period, with a median of 10 days between each injection. All injections were delivered according to previously described safety protocols.[7] Pigmentary retinopathy was noted superotemporally in the quadrant of intravitreal injections after 4 rounds of intravitreal melphalan (Fig. 2 [A]). Given sustained improvement in seeding and lack of macular toxicity, intravitreal therapy was continued, as the child's parents were adamant to not enucleate the eye given improvement in seeding with each subsequent exam The patient received 20ug of intravitreal melphalan for the first 7 cycles, and due to persistent seeding, this was followed by one cycle of 30ug of intravitreal melphalan. Thereafter the patient received combined intravitreal melphalan 20ug and topotecan 20ug therapy for an additional 7 cycles, as melphalan intravitreal monotherapy showed slow improvement with each exam under anesthesia and the addition of topotecan was thought to improve chances of clearance of vitreous seeds more rapidly. At the conclusion of treatment, the cumulative intravitreal dose of melphalan totaled 310ug, while the cumulative intravitreal dose of topotecan was 140umg.

Intravitreal chemotherapy was discontinued after 15 cycles when the patient was noted to have a retinal hole within the site of prior cryotherapy at the primary tumor scar. At that time there was mild and calcified, inactive-appearing vitreous seeding on funduscopic examination. The retinal hole was surrounded with laser (532 nm, Alcon Purepoint, Alcon Laboratories, Fort Worth, TX, USA). The patient was monitored with monthly EUAs for 6 months thereafter. The patient was then transitioned to office follow-up as she was cooperative enough for exam without anesthesia. The patient is now 7 years out from treatment completion without tumor recurrence (Fig. 2 [B]). Her final visual acuity is 20/50 in the treated eye left eye and 20/20 in the right eye with

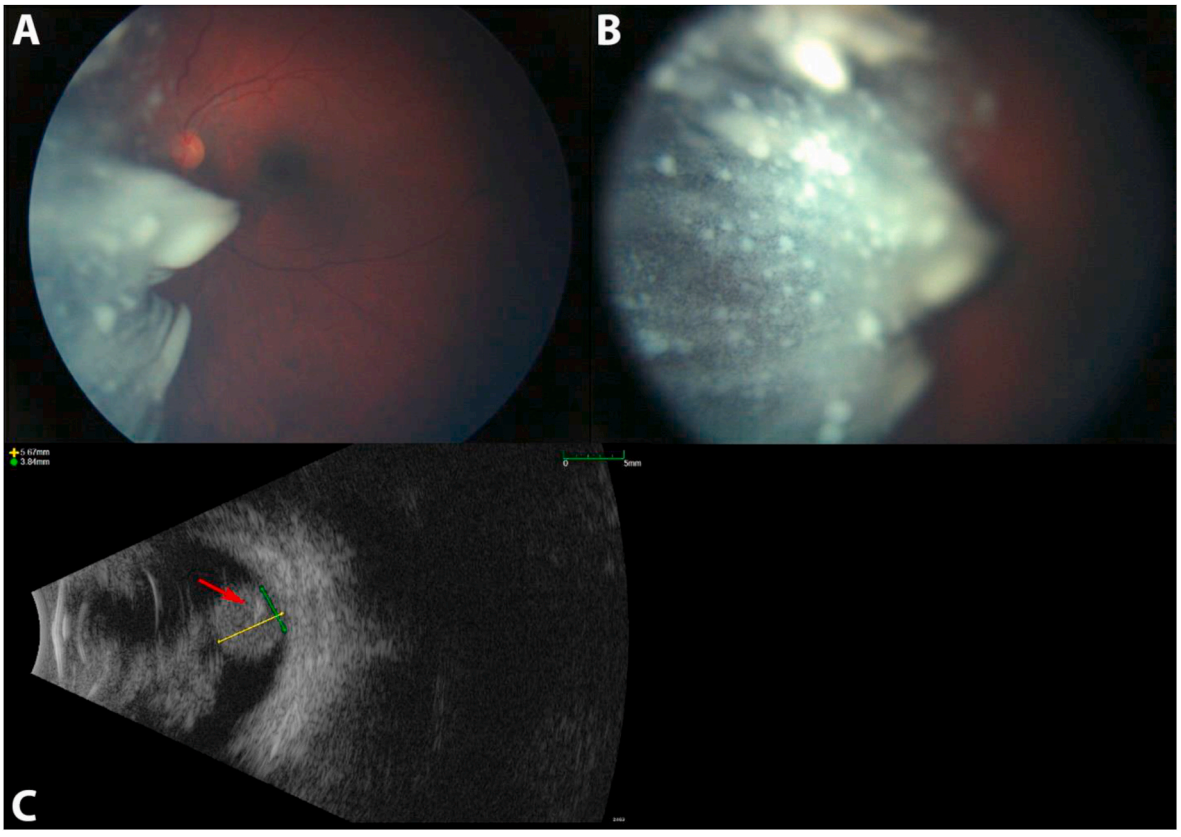

Fig. 1. Retinoblastoma imaging at presentation. (A) Retcam (Retcam 3, Natus, Middleton, WI, USA) fundus photograph demonstrating an endophytic tumor extending towards the vitreous cavity. (B) Retcam photograph of vitreous cavity demonstrating vitreous seeding ranging from clouds to dust. (C) B-scan ultrasound, transverse, in the 10 o'clock position, demonstrating endophytic mass (5.67mm height x 3.84mm width) with intralesional calcification (red arrow) and vitreous seeding. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

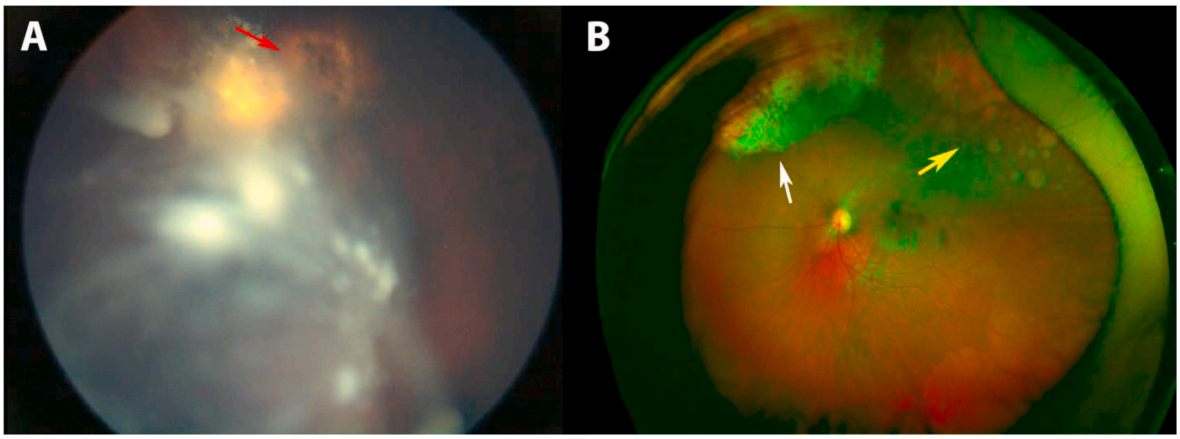

Fig. 2. Retinoblastoma imaging after treatment initiation. (A) Retcam fundus photograph demonstrating pigmentary retinopathy after 4 rounds of intravitreal melphalan. (B) Color fundus photograph taken 8 months after treatment completion demonstrating resolution of vitreous seeding. White arrow points to the area of prior cryotherapy. Yellow arrow points to persistent focus of pigmentary retinopathy. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

spectacle correction.

3. Discussion

Intravitreal chemotherapy has greatly impacted eye salvage rates in retinoblastoma. No randomized trials have explored adequate length of treatment for intravitreal chemotherapy. Currently, the number of intravitreal chemotherapy injections given to patients with vitreous seeding is based largely on historical experience rather than scientific evidence. We share the case of a patient who benefitted from a prolonged course of 15 intravitreal chemotherapy cycles with resolution of retinoblastoma vitreous seeding, excellent visual outcome, and limited retinal toxicity. While enucleation is always acceptable in an eye with non-clearing vitreous seeding, this patient's seeding improved at each examination, and her parents strongly declined enucleation, requesting continued intravitreal chemotherapy.

Adverse effects of intravitreal chemotherapy include pigmentary retinopathy, cataract formation, and retinal hemorrhages.[7,10,12] Shields et al. explored variable melphalan dosing (8-50μg) in human subjects and showed an 8ug dose was sub-therapeutic, and a 50ug dose led to intolerable side effects including cataracts, vitreous and subretinal hemorrhages, and phthisis bulbi.[13] The authors concluded that a 20-30μg dose, as established in preliminary animal studies,[9] was ideal for intravitreal melphalan treatment. Though increased injection dose leads to unacceptable adverse effects, no association has been found between the number of melphalan injections or cumulative melphalan dose and drug toxicity.[14,15] Some studies suggest an association between number of injections and decreased ERG response, however, these results have not been consistently replicated.[12,16] More recently, the addition of topotecan to melphalan for intravitreal treatment has shown promising results and has not been associated with increased drug toxicity, instead reducing the number of injections needed to achieve vitreous seeding resolution.[17] This patient developed pigmentary retinopathy after four doses of intravitreal melphalan. The retinopathy did not extend beyond the injection quadrant. Despite repeated intravitreal therapy, our patient did not experience further drug related toxicity and retained good visual acuity.

Beyond drug related toxicity, intravitreal chemotherapy injections have associated procedural risks including retinal detachments, endophthalmitis, and vitreous hemorrhage.[18] Thus treatment cycles should be limited to the lowest number of injections needed to achieve seeding resolution. Vitreous seeds are categorized by their morphologic appearance into dust, spheres, and clouds.[14] Francis et al. studied vitreous seeding based on morphological sub-type, showing that injection requirements increase incrementally with each seed subtype (dust < sphere < cloud).[19] Most cases of vitreous seeding resolved with a median of 3 intravitreal injections, with dense cloud seeding requiring a median of 6 injections until resolution.[20] However, a subset of patients will have persistent seeding beyond the accepted 6–8 injection cycles. In these cases, providers must decide whether to continue intravitreal chemotherapy or opt for salvage therapies, such as radiation or enucleation. This case demonstrates prolonged intravitreal chemotherapy may be considered prior to salvage therapies in eyes with good treatment response and limited drug toxicity.

Intravitreal chemotherapy treatment protocols vary by institution. Some centers opt for weekly intravitreal injections until seeding resolution is achieved or a maximum of 8 cycles is reached.[10,11] Other centers plan injection series of 2–4 injections each, observing patients for one month between series. Some investigators advocate for an additional consolidating injection to treat microscopic disease after gross seeding resolution is achieved.[7,21] Variation in treatment protocols arises from a lack of overarching guidelines for intravitreal therapy delivery. This patient had continued improvement in vitreous seeding after treatment cessation, suggesting intravitreal therapy might have continued effects that surpass standard one-week injection intervals. Improved understanding of intravitreal chemotherapy pharmacokinetics is needed to optimize drug loading, series duration, and recommended interval times between injection series.

4. Conclusion

Our case demonstrates that repeated intravitreal chemotherapy beyond 8 injections can be effective for the treatment of persistent vitreous seeding in retinoblastoma. Our patient was able to preserve a visual acuity of 20/50 after 15 cycles of intravitreal chemotherapy. We believe extended intravitreal chemotherapy may be considered prior to more invasive salvage therapies, such as radiation or enucleation, in eyes with good response to intravitreal therapy.

5. Patient consent

The patient's parents provided written consent for publication of this case report.

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Authorship

All authors attest that they meet the ICMJE criteria for Authorship.

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Declaration of competing interest

The authors have no conflict of interest.

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