

Management of Advanced Retinoblastoma with Intraarterial Chemotherapy

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Intraarterial chemotherapy has been heralded as an innovative targeted approach for the management of retinoblastoma.¹⁻³ This technique employs local delivery of chemotherapy to the eye at a concentration tolerable to the eye and sufficient to achieve tumor control. The desired biological effect is gained while presumably minimizing systemic side effects. Currently, there is no strict protocol for intraarterial chemotherapy, but the Children's Oncology Group is organizing a multicenter, collaborative, prospective trial to investigate the risks and benefits of this therapy. Most centers abide by a 3-cycle protocol and stratify dosage based on patient body mass and tumor response.¹ The overwhelming goal is to achieve control with as few cycles as possible to minimize toxicity to the eye and body.

Intraarterial chemotherapy is remarkably effective for retinoblastoma control, with reports of up to 100% globe salvage for retinoblastoma groups C and D.⁴ However, intraarterial chemotherapy has proven less effective for more advanced group E retinoblastoma, mostly due to persistent or recurrent vitreous and subretinal seeding. Seeding has historically been the source of most recurrences following chemotherapy, as noted with standard intravenous chemoreduction.⁵ In a study of 158 eyes with retinoblastoma managed with intravenous chemoreduction, 54 eyes manifested vitreous seeds on initial examination and recurrence was

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noted in 50% by 5 years. Of the 71 eyes with subretinal seeds on initial examination, 5-year recurrence was 62%.⁵ Seed recurrence can also be a problem following intraarterial chemotherapy treatment. In a study of 16 eyes with retinoblastoma treated with intraarterial chemotherapy, subretinal seed recurrence was noted in 18% and vitreous seed recurrence, in 33%.⁴ This article describes a case of advanced retinoblastoma (group D) with extensive subretinal and vitreous seeding that responded completely to 3 cycles of intraarterial chemotherapy using Melphalan.

CASE REPORT

A 26-month-old white male was referred with leukocoria from suspected retinoblastoma. Examination revealed normal right eye. The left eye displayed total retinal detachment with massive retinoblastoma filling

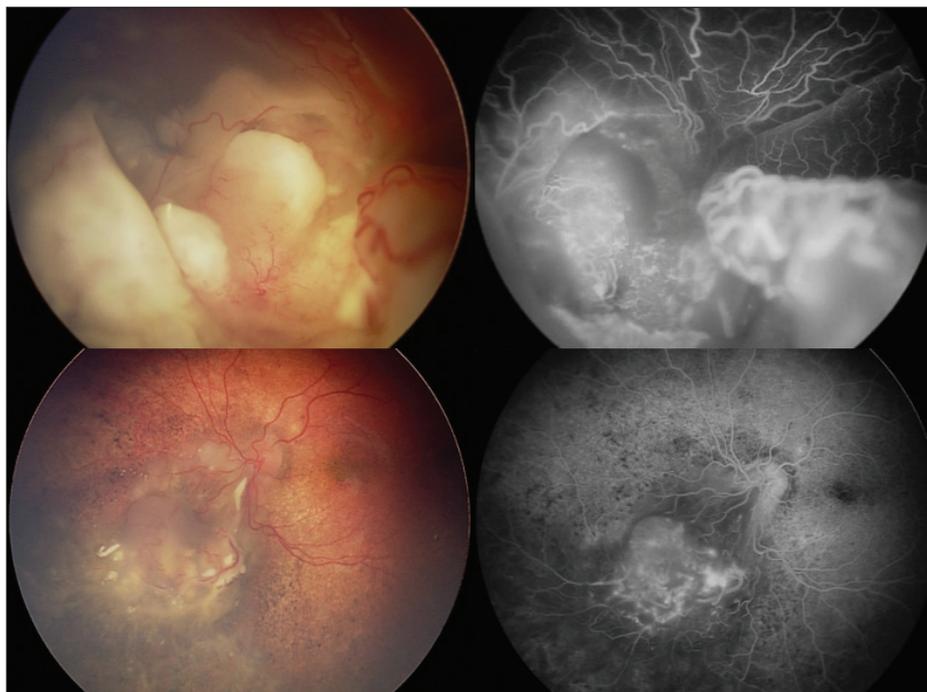


Figure 1. A 26-month-old white male with advanced group D retinoblastoma involving the inferior hemiretina and extending into the macular and epipapillary region, with extensive subretinal fluid and seeding and moderate vitreous seeding (A). Fluorescein angiography documents the retinal detachment and the vascular tumor (B). Following 3 sessions of intraarterial chemotherapy with Melphalan 5 mg dose, the retinal detachment has resolved and the tumor regressed (C). Following IAC, the fluorescein angiogram documents flat retina with regressed tumor (D).

the posterior segment of the eye and measuring 24 mm in diameter and 10 mm in thickness. The tumor was primarily located inferiorly, extending into the macula and overhanging the optic disc (Figure 1A). There was extensive subretinal seeding and mild vitreous seeding. This eye was classified as Group D retinoblastoma. Fluorescein angiography (Figure 1B) confirmed the tumor and suggested possible neovascularization of the retina and iris.

Management options included enucleation, intravenous chemoreduction, or intraarterial chemotherapy. Based on the unilateral involvement and hope for some return of visual acuity, intraarterial chemotherapy was performed. The intraarterial chemotherapy was delivered under general anesthesia via cannulation of the femoral artery and guided into the aorta, carotid artery, and facing the ostium of the ophthalmic artery. The intraarterial chemotherapy was repeated monthly for a total of 3 cycles using freshly prepared Melphalan 5 mg dose in 30 cc of saline. Following therapy, the retinal detachment completely resolved with intact macula (Figure 1C). The retinoblastoma regressed to a residual

calcified scar of 14-mm base and 2 mm in thickness. There were no local or systemic complications. The patient remains stable at 18 months' follow-up with meaningful vision in the involved eye, documented with patching therapy.

COMMENT

Enucleation has been and remains the standard management for advanced unilateral retinoblastoma, particularly those with neovascular glaucoma.⁶ Intraarterial chemotherapy is an alternative to enucleation. There are numerous benefits of intraarterial chemotherapy, including restoration of some visual acuity, especially if the tumor is extramacular in location. Additionally, intraarterial chemotherapy allows the child

to avoid the cosmetic and psychological challenges of an enucleated eye. It should be realized that intravenous chemoreduction is another alternative to enucleation, with potentially equivalent regression of the main tumors and similar risk as intraarterial chemotherapy for seed recurrence. Chemoreduction using vincristine, etoposide, and carboplatin provides tumor control with globe salvage in nearly 50% of group D eyes.⁷ Gunduz et al found that the main reasons for treatment failure following chemoreduction was subretinal seeding, vitreous seeding, and subretinal fluid, all features commonly found with group D retinoblastoma.⁸ However, it should be understood that powerful advantages of chemoreduction over intraarterial chemotherapy is the reduced risk for metastasis, pinealoblastoma, and long-term second malignant neoplasms.⁹

With regard to intraarterial chemotherapy, many eyes previously destined for enucleation have been salvaged. Abramson et al identified in an initial report that 7 of the 9 eyes avoided enucleation with intraarterial chemotherapy.⁹ Peterson et al studied 17 eyes

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with group D retinoblastoma that failed systemic chemotherapy and were treated with intraarterial chemotherapy, of which 13 (76%) were salvaged.¹¹ Shields et al found successful globe salvage with intraarterial chemotherapy in 100% of group C, 100% of group D, and 33% of group E eyes. The main reason for failure of chemotherapy, both intravenous and intraarterial routes, is recurrence of subretinal or vitreous seeding.^{1,2} It appears that intraarterial chemotherapy is somewhat more effective for subretinal seeding, compared with intravenous chemotherapy.¹ Abramson et al studied eyes with retinoblastoma seeding and found ocular salvage with primary intraarterial chemotherapy in 80%.¹² Complete regression of seeding with globe salvage was found in 83% eyes with subretinal seeding and 64% with vitreous seeding. Shields et al studied the effect of seeding on outcome and noted similar results, with intraarterial chemotherapy providing complete response in 82% of those with subretinal seeding and 67% with vitreous seeding.⁴ In our case, both subretinal and vitreous seeding were present and completely controlled with 3 doses of intraarterial chemotherapy.

Thus, it appears that intraarterial chemotherapy is a valuable therapy for globe preservation in children with retinoblastoma.^{9-11,13} However this technique should be used with caution as there are risks for cerebrovascular events that can be immediate, such as vascular spasm or occlusion, and can be long-term, yet to be realized. Furthermore, Melphalan can cause local side effects of eyelid edema, blepharoptosis, cilia loss, forehead redness, and temporary extraocular muscle dysfunction. Additional exposure to low-dose radiation from fluoroscopy as the arterial catheter courses the body can be problematic. For these reasons, attempting to minimize the number of intraarterial chemotherapy cycles is advised. Minimal exposure (<3 cycles) has been found to be sufficient for some Group C and D eyes, particularly those with minimal seeding.¹⁴ Last, and most important, intraarterial chemotherapy is a focal therapy with little effect in prevention of metastasis.¹³

At present, there is no standard approach for intraarterial chemotherapy.^{4,9,13} At the few centers with

capability to perform intraarterial chemotherapy, the chemotherapeutic agents, dosage, cycles, and technique varies slightly.^{1,13} However, the importance of intraarterial chemotherapy rests in its ability to provide lasting tumor control, as both a primary and secondary therapy, while minimizing adverse systemic outcomes.

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