Intravitreal Melphalan for Refractory or Recurrent Vitreous Seeding From Retinoblastoma

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Objective: To evaluate the efficacy and complications of intravitreal chemotherapy for viable vitreous seeding from retinoblastoma.

Methods: Intravitreal injection of melphalan (8-50 µg in 0.05 mL) followed by injection site cryotherapy.

Results: Among 12 treated cases, success with control of vitreous seeds was achieved in 10 of 12 cases at immediate follow-up (0-3 months), 8 of 10 cases at short-term follow-up (3-6 months), and 6 of 10 cases at long-term (>6 months) follow-up. Among those 8 cases that received an 8- to 10-µg dose, control was achieved in 6 of 8 cases at immediate follow-up, 5 of 7 cases at short-term follow-up, and 3 of 7 cases at long-term follow-up. Complications with the 8- to 10-µg dose were minor and included preretinal hemorrhage and retinal vasculitis with retinal pigment epithelial alterations. Of those 4 that received a 50-µg dose, immediate, short-term, and long-term control was 100%, but complications of cataract, vitreous hemorrhage, subretinal hemorrhage, severe hypotonia, and phthisis lead to enucleation in 2 cases. There was no case of orbital tumor recurrence or retinoblastoma metastasis (follow-up range, 8-66 months).

Conclusions: Intravitreal melphalan for recurrent vitreous seeds from retinoblastoma appears to provide vitreous seed control in some patients. A high dose (50 µg) of melphalan is toxic and should be avoided.

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RETINOBLASTOMA IS GENER- ally managed with systemic chemotherapy. According to the International Classification of Retinoblastoma, standard intravenous chemoreduction is successful for 100% of group A, 93% of group B, 90% of group C, 48% of group D, and 25% of group E eyes. Adjuvant low-dose radiotherapy improves globe salvage of group E eyes to 83%. A newer method of intra-arterial chemotherapy has shown promise for salvage of group D and E eyes. One of the most challenging aspects of retinoblastoma therapy is control of persistent or recurrent viable vitreous or subretinal tumor seeds. A previous report on vitreous seed control revealed eye salvage in 64% of patients treated with chemotherapy (using carboplatin, etoposide, and vincristine) and whole-eye radiotherapy at 5 years. Intra-arterial chemotherapy offers control for subretinal seeds in 82% of patients and for vitreous seeds in 67% of patients. A few reports on intravitreal chemotherapy for viable vitreous seeds have been published using thiotepa, melphalan, and methotrexate. Herein, we share our experience with intravitreal melphalan in 12 eyes with viable retinoblastoma vitreous seeds.

METHODS

Approval for this retrospective study was received by the Farabi Hospital Review Committee of Tehran University of Medical Sciences, Tehran, Islamic Republic of Iran, and by institutional review board of Wills Eye Institute, Thomas Jefferson University, Philadelphia, Pennsylvania. Criteria for inclusion were eyes with viable vitreous seeds for which standard chemotherapy and/or radiotherapy methods failed and for which enucleation was the remaining option. Success was defined as stabilization or regression of vitreous seeds and was categorized into immediate, (0-3 months) short-term (3-6 months), and long-term (>6 months) control. Failure was defined as growth of vitreous seeds or appearance of new vitreous seeds based on fundu-
scopic examination (Figure 1 and Figure 2). After informed consent, under sterile technique, intravitreal melphalan (8-50 µg in 0.05 mL) was prepared in the operating room. Dosages were initiated at 8 µg in the first 2 patients (by C.L.S.), and

Figure 1. Vitreous seed control with low-dose (8 µg) intravitreal melphalan. A and B, Following chemoreduction and external beam radiotherapy delivered elsewhere, this patient was referred with approximately 70 viable recurrent vitreous seeds appearing as soft white translucent tumors floating in the vitreous gel. Melphalan at a dose of 8 µg was injected into the vitreous by transcorneal route. C and D, Two weeks after the first injection, the seeds are nearly resolved. E and F, Four months after 8 injections, the seeds are completely resolved, leaving clear vitreous.
later dosage increase was explored (by F.G.) owing to poor control, and dosage was adjusted based on amount of seeding. The freeze-dried powder melphalan (Alkeran; Aspen Pharmacare Australia Pty Ltd) was prepared using the provided sterile diluent. The medication was immediately injected through the peripheral cornea and iris root (at Wills Eye Institute) into anterior vitreous or through the pars plana (3 mm from limbus, beveled approach) (at Farabi Hospital) superotemporally using 30-gauge needle (Table). Cryotherapy at injection site was performed as single freeze-thaw cycle. There was no aqueous humor tap. Forceps-induced globe jiggling for 10 seconds to disperse vitreous chemotherapy was performed. Intraocular pressure was monitored 2 hours after injection and at each follow-up. Patient examination was performed every 3 to 4 weeks under general anesthesia with repeated injection if needed at the time of examination under anesthesia until vitreous seed control was achieved.

RESULTS

Over the past 6 years, 12 eyes of 12 patients received intravitreal melphalan for active vitreous seeding from retinoblastoma (Table). All patients had received 6 to 8 cycles of standard chemotherapy, and 2 received addi-
Intravitreal chemotherapy was explored by Ericson and Rosengren in 1961 using thiopeta for treatment of retinoblastoma in 6 cases, achieving success in 4 cases. They further investigated intravitreal injection of several chemotherapeutic agents in rabbit eyes using nitrogen mustard, cyclophosphamide, methotrexate, and thiopeta and established ocular toxicity levels. Inomata and Kaneko found in vitro that retinoblastoma was most sensitive to melphalan, compared with vincristine, bleomycin, 5-fluorouracil, methotrexate, dacarbazine, and cytosine arabinoside. Kaneko performed intravitreal injection of 8- to 30-µg of melphalan combined with ocular hyperthermia for vitreous tumor seeding in 41 eyes, and unpublished results revealed an eye-preservation rate of nearly 51%. Munier studied 23 seeding in 41 eyes, and unpublished results revealed an combined with ocular hyperthermia for vitreous tumor complications with an 8- to 10-µg dose were minor and included preretal hemorrhage (n=1) and retinal vasculitis with retinal pigment epithelial alterations (n=1). Of those 4 patients who received the 50-µg dose, immediate, short-term, and long-term control was 100%, but complications of cataract, vitreous hemorrhage, subretinal hemorrhage, severe hypotonia, and phthisis lead to enucleation in 2 cases. There were no viable vitreous seeds histopathologically. Of the total 12 eyes, all facing enucleation as the main alternative, 4 were ultimately spared enucleation by intravitreal melphalan. The 8 that came to enucleation were for reasons of new retinoblastoma (n=1), recurrent solid retinoblastoma and vitreous seeds (n=2), recurrent vitreous seeds (n=2), phthisis bulbi (n=2), and chemotherapy intolerance/family preference (n=1). There were no cases of orbital or systemic retinoblastoma recurrence over a mean 32 months’ follow-up (median, 32.5 months; range, 8-66 months).

In conclusion, our mean 3-year experience shows that intravitreal melphalan for recurrent vitreous retinoblastoma seeds following failed systemic chemotherapy appears to provide vitreous seed control in some patients. Further studies on pharmacokinetics of vitreous melphalan at varying dosages and the anticipated complications should be performed. Investigation should be made into more effective agents with a longer half-life and higher therapeutic indices. From this small cohort, it appears that a high dose (50 µg) of melphalan is toxic and should be avoided.

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REFERENCES