Intravitreal Melphalan for Refractory or Recurrent Vitreous Seeding From Retinoblastoma

Fariba Ghassemi, MD; Carol L. Shields, MD

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 ptosis 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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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
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-

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**Table. Outcomes of 12 Patients With Retinoblastoma and Refractory or Recurrent Vitreous Tumor Seeding Managed With Intravitreal Melphalan**

<table>
<thead>
<tr>
<th>Variable</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
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</thead>
<tbody>
<tr>
<td>Age at time of diagnosis, mo</td>
<td>23</td>
<td>84</td>
<td>6</td>
<td>9</td>
<td>24</td>
<td>24</td>
<td>12</td>
<td>24</td>
<td>17</td>
<td>11</td>
<td>50</td>
<td>33</td>
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<tr>
<td>Affected eye</td>
<td>OS</td>
<td>OS</td>
<td>OS</td>
<td>OU</td>
<td>OD</td>
<td>OS</td>
<td>OU</td>
<td>OS</td>
<td>OU</td>
<td>OD</td>
<td>OS</td>
<td>OS</td>
</tr>
<tr>
<td>ICRB group in treated eye</td>
<td>D</td>
<td>D</td>
<td>C</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
<td>D</td>
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<td>D</td>
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<tr>
<td>Previous therapy cycles</td>
<td>4</td>
<td>72</td>
<td>24</td>
<td>17</td>
<td>8</td>
<td>7</td>
<td>7</td>
<td>18</td>
<td>9</td>
<td>9</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Interval VEC start to recurrent vitreous seeds, mo</td>
<td>IVM</td>
<td>IVM</td>
<td>IVM + IVB</td>
<td>IVM</td>
<td>IVM</td>
<td>IVM + IVB</td>
<td>IVM</td>
<td>IVM</td>
<td>IVM</td>
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<tr>
<td>IVM dose, µg</td>
<td>8</td>
<td>8</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>50</td>
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<tr>
<td>IVM cycles</td>
<td>8</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>2</td>
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<tr>
<td>IVM approach</td>
<td>Co</td>
<td>Co</td>
<td>PP</td>
<td>PP</td>
<td>PP</td>
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<tr>
<td>Outcome ^b</td>
<td>Success</td>
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<tr>
<td>Complications</td>
<td>Retinal vasculitis, RPE mottling</td>
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<td>None</td>
<td>None</td>
<td>None</td>
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<tr>
<td>Other therapy after IVM (mo)</td>
<td>Enuc (12)</td>
<td>Enuc (7)</td>
<td>Enuc (3)</td>
<td>None</td>
<td>Enuc (5)</td>
<td>Enuc (5)</td>
<td>Enuc (7)</td>
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<td>None</td>
<td>Enuc (3)</td>
<td>Enuc (8)</td>
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<tr>
<td>Reason for other therapy after IVM</td>
<td>Recurrent vitreous seeds</td>
<td>Recurrent vitreous seeds</td>
<td>New RB</td>
<td>None</td>
<td>Recurrent solid RB and vitreous seeds</td>
<td>None</td>
<td>Recurrent solid RB</td>
<td>None</td>
<td>Chemotherapy intolerance</td>
<td>Phthisis</td>
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<td>Local RB recurrence in orbit</td>
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<td>None</td>
<td>None</td>
<td>None</td>
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<td>None</td>
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<td>None</td>
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<td>None</td>
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<tr>
<td>Metastatic RB (months’ follow-up)</td>
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<td>None (66)</td>
<td>None (37)</td>
<td>None (34)</td>
<td>None (32)</td>
<td>None (27)</td>
<td>None (23)</td>
<td>None (18)</td>
<td>None (14)</td>
<td>None (35)</td>
<td>None (8)</td>
<td>None (33)</td>
</tr>
</tbody>
</table>

Abbreviations: Co, cornea; EBRT, external beam radiotherapy; EC, etoposide and carboplatin; enuc, enucleation; ICRB, International Classification of Retinoblastoma; IVB, intravitreal bevacizumab; IVM, intravitreal melphalan; OD, right eye; OS, left eye; phthisis, phthisis bulbi; PP, pars plana; preret seed, preretinal hemorrhage; PS, posterior synchysis; RB, retinoblastoma; RPE, retinal pigment epithelial; VEC, vincristine, etoposide, and carboplatin; vit hemo, vitreous hemorrhage.

^a Two first cases were treated in Philadelphia, Pennsylvania, and the rest in Tehran, Islamic Republic of Iran.

^b Months’ follow-up after starting IVM; success is stabilization or regression of vitreous seeds, and failure is recurrent seeds or growth of seeds.

^c Then recurrent vitreous seeds.
tional external radiotherapy. At the time of injection, no patient was on systemic chemotherapy. Following injection, there was no prolonged elevation of intraocular pressure.

Overall, success with control of vitreous seeds was achieved in 10 of 12 cases (83%) at immediate follow-up, 8 of 10 cases (80%) at short-term follow-up, and 6 of 10 cases (60%) at long-term follow-up. Among those 8 cases that received an 8- to 10-µg dose, control was achieved in 6 of 8 cases (75%) at immediate follow-up, 5 of 7 cases (71%) at short-term follow-up, and 3 of 7 cases (43%) at long-term follow-up. Complications with an 8- to 10-µg dose were minor and included preretinal 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 hypotony, and phthisis led 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).

**COMMENT**

Intravitreal chemotherapy was explored by Ericson and Rosengren in 1961 using thiotapec for treatment of retinoblastoma in 6 cases, achieving success in 4 cases. They further investigated intravitreal injection of several chemotherapy agents in rabbit eyes using nitrogen mustard, cyclophosphamide, methotrexate, and thiotapec and established ocular toxicity levels. They observed the main adverse effect of vitreous opacification.

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 doses 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 advanced retinoblastoma. All were treated with intraocular chemotherapy/external radiotherapy for advanced retinoblastoma. They observed the main adverse effect of vitreous opacification.

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**