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 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.

Arch Ophthalmol. 2012;130(10):1268-1271

Retinoblastoma is generally 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
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-

<table>
<thead>
<tr>
<th>Variable</th>
<th>Case No.</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>
</tr>
</thead>
<tbody>
<tr>
<td>Age at time of diagnosis, mo</td>
<td></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>
</tr>
<tr>
<td>Affected eye</td>
<td></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></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>
<td>D</td>
<td></td>
</tr>
<tr>
<td>Pretherapy (cycles)</td>
<td></td>
<td>VEC (9), EBRT</td>
<td>VEC (8), EBRT</td>
<td>VEC (8)</td>
<td>VEC (8)</td>
<td>VEC (7)</td>
<td>VEC (6)</td>
<td>VEC (8)</td>
<td>VEC (6)</td>
<td>VEC (8)</td>
<td>VEC (6)</td>
<td>VEC (7)</td>
<td></td>
</tr>
<tr>
<td>Interval VEC start to recurrent</td>
<td></td>
<td>4</td>
<td>4</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>Treatment vitreous seeds, µg</td>
<td></td>
<td>IVM</td>
<td>IVM</td>
<td>IVM</td>
<td>IVM</td>
<td>IVM</td>
<td>IVM</td>
<td>IVM</td>
<td>IVM</td>
<td>IVM</td>
<td>IVM</td>
<td>IVM</td>
<td>IVM</td>
</tr>
<tr>
<td>IVM cycles</td>
<td></td>
<td>8</td>
<td>8</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>IVM approach</td>
<td></td>
<td>Co</td>
<td>Co</td>
<td>PP</td>
<td>PP</td>
<td>PP</td>
<td>PP</td>
<td>PP</td>
<td>PP</td>
<td>PP</td>
<td>PP</td>
<td>PP</td>
<td>PP</td>
</tr>
<tr>
<td>Outcome b</td>
<td></td>
<td>Success for 1 y c</td>
<td>Success for 7 mo c</td>
<td>Success</td>
<td>Success</td>
<td>Failure</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
<td>Success</td>
</tr>
<tr>
<td>Complications</td>
<td></td>
<td>Retinal vasculitis, RPE mottling</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Other therapy after IVM (mo)</td>
<td></td>
<td>Enuc (12)</td>
<td>Enuc (7)</td>
<td>Enuc (3)</td>
<td>None</td>
<td>Enuc (5)</td>
<td>None</td>
<td>Enuc (5)</td>
<td>None</td>
<td>Enuc (7)</td>
<td>None</td>
<td>Enuc (3)</td>
<td>Enuc (8)</td>
</tr>
<tr>
<td>Reason for other therapy after IVM</td>
<td></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>
<td>None</td>
<td>Phthisis</td>
</tr>
<tr>
<td>Local RB recurrence in orbit</td>
<td></td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Metastatic RB</td>
<td></td>
<td>None (60)</td>
<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; IVM, intravitreal melphalan; OD, right eye; OS, left eye; phthisis, phthisis bulbi; PP, pars plana; preret seed, preretinal hemorrhage; PS, posterior synchia; 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.

©2012 American Medical Association. All rights reserved.

Downloaded From:  by a Non-Human Traffic (NHT) User on 11/02/2018
Intravitreal chemotherapy was explored by Ericson and Rosengren in 1961 using thiotepa 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 thiotepa 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 ocular toxicity rate of nearly 51%. Munier studied 23 cases of recurrent vitreous seeds treated with up to 8 weekly intravitreal melphalan (8-30 µg) injections and found 87% control at 17 months. Although it is difficult to accurately compare results with unpublished data, this information is the only available data at this time. The 2 unpublished series mentioned above used 8 to 30 µg of melphalan. Because there is no published data, we cannot compare complications by dosage.

In our 12 cases, the patients were facing enucleation and had received numerous previous treatments of systemic chemotherapy/external radiotherapy for advanced retinoblastoma. All were treated with intravitreal melphalan for recurrent vitreous seeds. Of those 8 eyes that received 8- to 10-µg doses of melphalan, vitreous seed control was found in 71% of cases at short-term follow-up and 43% of cases at long-term follow-up, and there were minor ocular toxicities. For the 4 eyes that received a 50-µg dose, control was achieved in 100% cases at both short-term and long-term follow-up, but serious adverse effects of hypotony/phthisis bulbi were noted. There was no case of orbital tumor recurrence or retinoblastoma metastasis. There was no tumor in the needle tract on histopathology in any eye that came to enucleation. A more detailed histopathologic study of these eyes will be published separately.

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.

Submitted for Publication: December 23, 2011; final revision received May 3, 2012; accepted May 7, 2012.

Correspondence: Carol L. Shields, MD, Ocular Oncology Service, Wills Eye Institute, 840 Walnut St, Ste 1440, Philadelphia, PA 19107 (carol.shields@shieldsoncology.com).

Financial Disclosure: None reported.

REFERENCES