Anterior Segment Seeding in Eyes With Retinoblastoma Failing to Respond to Intraophthalmic Artery Chemotherapy

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Methods

A retrospective clinicopathologic review of enucleated eyes with retinoblastoma that had failed to respond to IAC was assembled from the pathology departments at University College London Institute of Ophthalmology and the Retinoblastoma Service, Royal London Hospital between March 1, 2010, and October 31, 2013. Data analysis was conducted from June 1, 2014, to March 1, 2015. The Clinical Effectiveness Unit of Barts Health National Health Service Trust approved the study (No. 6222), granting consent for collection and analysis for this study and waiving the need for patient consent. Indications for enucleation included the presence of clinically viable tumor or complications after multiple treatments.

After harvest of fresh tumor for genetic analysis, eyes were fixed in neutral buffered formalin and processed with sections stained with hematoxylin-eosin for light microscopy. Microscopic sections included the pupil and optic nerve, with
multiple sections through both calottes and a transverse section from the optic nerve at the surgical margin.

Results
A total of 12 eyes with retinoblastoma that had failed to respond to IAC were enucleated from 11 patients during the study period. There were 8 males and 4 females (6 left and 6 right eyes). The mean (median [range]) age at first diagnosis was 36 (12 [4-147]) months and, at the time of the first IAC treatment, 57 (39 [14-151]) months. The International Classification of Retinoblastoma group was B in 1 eye (8%), C in 4 eyes (33%), and D in 7 eyes (58%). A germline mutation was found in 6 of 11 patients (55%). Systemic chemotherapy, with a minimum of vincristine sulfate, etoposide, and carboplatin, was not effective in 10 patients (91%), and IAC was a secondary treatment; IAC was the primary treatment in only 1 case (9%).

Features requiring IAC included vitreous seeding in 11 eyes (92%), edge relapse in 6 eyes (50%), and multiple viable tumors in 1 eye (8%). All patients received IAC with single-agent melphalan hydrochloride, with successful catheterization of the ostium of the ophthalmic artery. The melphalan hydrochloride dose was 5.0 mg in 11 eyes (92%) and 10.0 mg in 1 eye (8%); the dose in another eye was increased from 5.0 mg to 7.5 mg after the second cycle. The number of cycles of IAC was 1 in 2 eyes (17%), 2 in 4 eyes (33%), 3 in 3 eyes (25%), 4 in 1 eye (8%), and 6 in 2 eyes (17%). Six of the 12 eyes (50%) received other treatments, including cryotherapy in 5 eyes (42%), laser ablation in 2 eyes (17%), external beam radiotherapy in 3 eyes (25%), and plaque brachytherapy in 4 eyes (33%). Clinical complications of IAC included third cranial nerve palsy (3 eyes [25%]), vitreous hemorrhage (4 eyes [33%]), iris neovascularization (1 eye [8%]), retinal pigment epithelial changes (2 eyes [17%]), retinal detachment (2 eyes [17%]), madarosis (1 eye [8%]), supratrochlear skin rash (2 eyes [17%]), and phthisis bulbi (1 eye [8%]).

Clinical indications (Figure 1 and Figure 2) for secondary enucleation were tumor viability and tumor seeding in the anterior segment in 6 eyes (50%), iris neovascularization in 6 eyes (50%), and neovascular glaucoma and vitreous hemorrhage in...
2 eyes each (17%). In 6 eyes (50%), involvement of the anterior chamber was apparent clinically, with tumor seeds floating in the anterior chamber and overlying the iris.

On histopathologic examination (Table and Figures 1 and 2), 4 of 12 eyes (33%) had no microscopic evidence of viable retinal tumors. In the remainder of the eyes, the retinoblastomas were graded as poorly (6 eyes [50%]) to moderately (2 eyes [17%]) differentiated.

Histopathologic involvement of the anterior segment was found in 8 of the 12 eyes (67%). This included eyes with involvement of the ciliary body and/or ciliary muscle (7 eyes [58%]), iris (6 eyes [50%]), and cornea (4 eyes [33%]). Three eyes (25%) had a small focus of tumor at the optic nerve head, but no tumors invaded the postlaminar optic nerve. No birefringent foreign material was found on polarization microscopy in any eyes. All cases with established high-risk retinoblastoma characteristics received adjuvant systemic chemotherapy.

Discussion

Intraophthalmic artery chemotherapy has received increasing attention since reports have shown good rates of tumor control and acceptable adverse effects. Persistent or recurrent viable vitreous or subretinal tumor seeds are the most difficult aspects of eye-preserving retinoblastoma therapy. Intraophthalmic artery chemotherapy offered control for 82% of the cases without subretinal seeds but only 64% to 67% for those with vitreous seeds. In the present series, we aim to contribute further to our understanding of treatment failure with IAC with the histopathologic findings of eyes with refractory retinoblastoma that required enucleation and demonstrate that anterior segment invasion occurred in 50% of the cases (6 eyes) on clinical grounds and 67% of the cases (8 eyes) on histopathologic analysis.

The indications for post-IAC enucleation are a combination of whether IAC was primary or secondary treatment, nonresponse, relapse, vitreous seeding, IAC complications, and threshold for enucleation. Persistence of vitreous seeds was the main reason for failure of eye preservation after IAC, which is in agreement with other reports. However, despite vitreous seeds described in those reports, anterior segment involvement was absent in contrast to our observations. In the present series, we also noted vitreous seeding but had the additional feature of tumor involvement of the ciliary body or muscle, iris, and cornea with active retinoblastoma in 67% of the cases (8 eyes). In fact, this situation has been reported previously after IAC in only 2 isolated cases; in one there was initial anterior chamber invasion that recurred and in the other involvement was documented on ultrasonographic biomicroscopy.

Vitreous seeds may persist after IAC for several reasons. The lack of vitreous blood flow and presence of blood-retinal barrier may prevent therapeutic IAC concentrations, but inactive vitreous seeds and drug resistance may also contribute. In one series, complete response after IAC was achieved in only 67% of the patients with vitreous seeds.
Seeding in Retinoblastoma After Failed Intraophthalic Chemotherapy

**Table. Histopathologic Findings of Anterior Segment Seeding After Failure of Intraophthalic Artery Chemotherapy**

<table>
<thead>
<tr>
<th>Eye</th>
<th>Neovascularization</th>
<th>Anterior Chamber Involvement of Retinoblastoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No</td>
<td>Ciliary body, iris, cornea</td>
</tr>
<tr>
<td>2</td>
<td>No</td>
<td>Ciliary muscle</td>
</tr>
<tr>
<td>3</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>Yes</td>
<td>Ciliary body, iris, anterior chamber, cornea</td>
</tr>
<tr>
<td>6</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>No</td>
<td>Retinoblastoma cells between the ciliary processes but not invading the ciliary body</td>
</tr>
<tr>
<td>9</td>
<td>Yes</td>
<td>Iris, iridocorneal angle, ciliary body</td>
</tr>
<tr>
<td>10</td>
<td>No</td>
<td>Ciliary body, iris</td>
</tr>
<tr>
<td>11</td>
<td>Yes</td>
<td>Ciliary body, iris, iridocorneal angle, trabecular meshwork, anterior chamber, cornea</td>
</tr>
<tr>
<td>12</td>
<td>Yes</td>
<td>Iris, cornea</td>
</tr>
</tbody>
</table>

Furthermore, treatment with chemotherapy may result in partial tumor necrosis and may cause seeds to disperse and travel anteriorly. Our histopathologic observations indicated a variable response of the main tumor with 4 eyes (33%) achieving retinal tumor control, but there was anterior tumor seeding of the ciliary body or muscle, iris, or cornea in 8 of the 12 cases (67%). These findings suggest that IAC has greater efficacy in posterior segment disease.

Our cases may be more aggressive than most, since we had a higher-than-expected prevalence of germline tumors (6 patients [55%]). In addition, these eyes received IAC using melphalan monotherapy. With additional topotecan hydrochloride therapy, results may be improved. Control of vitreous seeding has been achieved by the introduction of a safety-enhanced technique for intravitreal chemotherapy delivery, and this is now the preferable modality for treatment of vitreous seeding.14

**Conclusions**

Intraophthalic artery chemotherapy has shown considerable promise in eye-salvaging treatment and is useful in the armamentarium against retinoblastoma. Anterior structures can become involved after IAC, even subclinically, meritling careful case selection and long-term follow-up.

**REFERENCES**


