tory system during air/fluid exchange if the air had direct access to the venous circulatory system.

The clinical situation is further complicated by a patent foramen ovale (which is present in 23%-45% of adults, based on autopsy studies). A patent foramen ovale allows trapped air to access the arterial circulatory system through the opening between the right and left atrium. This can result in air emboli throughout the systemic arterial circulatory system, causing cerebral, cardiac, and visceral infarction, as occurred in the second case.

Treatment of VAE consists of immediately flooding the operative field with fluid to stop entry of the air. Additional measures would be at the discretion of the anesthesiologist and include increasing inspired oxygen, discontinuing nitrous oxide, if it is being used, inotropic support, and aspiration of air if a right atrial catheter has been placed. Although this complication is rare, ophthalmologists should be aware that it can occur during an air/fluid exchange, especially in the setting of significant trauma. During retinal cases, the anesthesiologist may not be fully aware of maneuvers happening within the eye, and the operating surgeon may be the first to recognize this problem if a patient becomes hemodynamically unstable after an air/fluid exchange is initiated. Promptly terminating the air infusion and returning the eye to a fluid filled state may help avoid systemic morbidity.

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Clinicopathologic Review of Enucleated Eyes After Intra-arterial Chemotherapy With Melphalan For Advanced Retinoblastoma

Retinoblastoma is a rare disease with only 250 to 300 cases diagnosed per year in the United States. Over the last 15 to 20 years, the long-term survival rates have been up to 99% in the developed world with aggressive treatment including systemic chemotherapy combined with focal laser therapy. Newer treatment techniques are focused on global conservation while minimizing toxic systemic adverse effects such as myelosuppression, need for blood transfusions, infections, and increased incidence of secondary tumors. One of these newer treatment techniques includes intra-arterial chemotherapy infusion of melphalan. This supraselective intra-ophthalmic artery chemotherapeutic drug delivery has been shown to be successful by Yamane et al and Abramson et al in advanced intraocular retinoblastoma (Reese-Ellsworth group V) cases. Herein, we report the clinicopathologic analysis of 3 eyes of 3 patients diagnosed with advanced retinoblastoma, Reese-Ellsworth group Vb, or International Classification of Retinoblastoma group D, treated with supraselective intra-ophthalmic artery infusion of melphalan at our institution by a technique previously described by Abramson et al. The patients underwent enucleation for evidence of tumor progression.

Report of Cases. Case 1. A 21-month-old girl was referred for worsening exotropia. On clinical examination, she was able to fix and follow objects with her right eye, and there was no response with the left eye. Leukocoria, a trace afferent pupillary defect, and intermittent exotropia were noted in the left eye. On dilated funduscopic examination, a peripapillary tumor extending through the fovea with secondary exudative retinal detachment was noted in the left eye. Subretinal and fine vitreous seeding was also noted (Figure 1A). The right eye was unremarkable. The patient was diagnosed with Reese-Ellsworth group Vb retinoblastoma in the left eye, with a normal systemic workup. Systemic chemotherapy was initiated with 4 agents (carboplatin, vincristine, etoposide, and cyclosporine) combined with focal laser therapy initially planned for 9 cycles but extended to 11 cycles based on tumor nonresponse. Subsequently, 6 cycles of periocular carboplatin injections (20-mg dose) were administered. Despite aggressive globe-conserving treatment, the tumor progressed (Figure 1B). Salvage treatment with intra-arterial melphalan infusion was administered at a 3-mg dose initially and then a 7.5-mg dose. On follow-up examination, vitreous hemorrhage was noted obscuring the tumor, with tumor progression evident on echographic imaging. The left eye was enucleated (Figure 1C).

Histopathologic examination disclosed an undifferentiated tumor present in primarily an exophytic configuration arising from the neural retina. The tumor was staged pT2c (pTNM staging) because it extended into the optic nerve to the level of the lamina cribrosa (Figure 1D), focally into the choroid (Figure 1E), and into the vitreous cavity. No tumor was present within the anterior chamber or at the
surgical margins. No rosettes or fleurettes were observed. Pseudorosettes were identified with foci of necrosis surrounding the viable tumor (Figure 1F). Foci of calcification were present subjacent to the tumor. The tumor was approximately 85% viable.

Case 2. A 3-year-old girl was referred for leukocoria and esotropia in the left eye. On clinical examination, the visual acuity was 20/25 OD and counting fingers OS. Dilated funduscopic examination revealed an unremarkable right eye and an exophytic, multifocal retinoblastoma involving the macula with secondary inferior retinal detachment and vitreous seeding (Figure 2A). She was diagnosed with Reese-Ellsworth group Vb retinoblastoma in the left eye. Further systemic workup was normal. Globe-conserving treatment of 9 cycles of systemic chemotherapy (carboplatin, vincristine, etoposide, and cyclosporine) combined with focal laser therapy was administered. There was marked reduction in the size of the largest tumor, with resolution of the complex exudative retinal detachment; however, a new focus of tumor in a peripapillary location was noted (Figure 2B). As a result, the patient underwent 3 cycles of carboplatin periocular injection at a 20-mg dose combined with focal laser treatment. The peripapillary tumor continued to progress (Figure 2C). The patient then received a 5-mg dose of intra-arterial melphalan infusion. Despite this treatment, the peripapillary tumor persisted. There was a concern for optic nerve invasion (Figure 2D), and the left eye was subsequently enucleated.

Histopathologic examination disclosed a peripapillary, undifferentiated tumor measuring 13 × 2 mm with vitreous seeding (Figure 2E). The tumor extended to the full thickness of the retina in a variable endophytic pattern and into the superficial optic nerve anterior to the level of the lamina cribrosa. Necrotic cellular debris was identified in the vitreous cavity. The subarachnoid space and choroid were free of tumor. The tumor was staged pT2a (pTNM). No rosette or fleurette formation was seen within the tumor. Approximately 30% of the tumor was viable (Figure 2F).

Case 3. An 11-month-old boy was referred for right leukocoria. On clinical examination, an exophytic, multifocal retinoblastoma with vitreous seeding in the posterior pole with obscuration of the optic nerve was observed in the right eye (Figure 3A). A small, multifocal retinoblastoma in the posterior pole was noted in the left eye without evidence of vitreous seeding. He was diagnosed with Reese-Ellsworth group Vb retinoblastoma in the right eye and group IIb in the left eye, with a normal systemic workup. Nine cycles of systemic chemotherapy (carboplatin, vincristine, etoposide, and cyclosporine) combined with focal laser therapy were performed. A marked tumor response with systemic chemotherapy was noted initially; however, tumor progression continued in both eyes (Figure 3B). An intra-ophthalamic artery infusion of 5 mg of melphalan in the right eye and 3 mg in the left eye was administered. Subsequently, because of residual tumor activity, the right eye was retreated with 7.5 mg of melphalan. On follow-up examina-

![Figure 1. Patient 1 presented with a large retinal tumor involving the posterior pole with associated exudative retinal detachment and vitreous seeding (A). After systemic chemoreduction and focal laser photocoagulation and periocular carboplatin injections, tumor growth was noted in the superonasal macula (B). As a salvage therapy, intra-arterial melphalan infusion was performed. At 6 months, dense postoperative vitreous hemorrhage continued to obscure direct tumor visualization (C). The patient underwent enucleation because tumor growth was noted on ultrasonography. Histopathologic examination disclosed an undifferentiated tumor (asterisk) extending into the optic nerve to the level of the lamina cribrosa (arrow) (D) (hematoxylin-eosin, original magnification ×40) and focally into the choroid (double arrows) (E) (periodic acid-Schiff, original magnification ×200). Pseudorosettes (white asterisk) were identified with foci of necrosis (black asterisk) surrounding a viable tumor (F) (hematoxylin-eosin, original magnification ×100).](https://archopht.jamanetwork.com/)
tion, the right eye showed tumor progression with globular vitreous seeding and an enucleation was performed (Figure 3C). The left eye was stable without tumor activity.

Microscopic examination showed a differentiated, multifocal retinal tumor present in a combined exophytic and endophytic configuration (Figure 3D). The tumor was well differentiated with approximately 40% viability. Flexner-Wintersteiner and Homer Wright rosettes as well as fleurettes were present (Figure 3E). A moderate amount of calcification was present within the tumor. The posterior aspect of the tumor extended to within 1.0 mm of the optic nerve but did not invade the optic nerve head. Foci of a viable tumor were present within the vitreous cavity (vitreous seeding). The tumor did not extend into the choroid or anterior segment and was staged pT1 (pTNM staging).

In all 3 cases, histopathologic evaluation of other ocular structures, including the optic nerve, retina, choroid, and associated vasculature, was otherwise unremarkable.

Comment. The supraselective intra-arterial infusion of the ophthalmic artery with a chemotherapeutic agent has been well described by Yamane et al and recently studied by Abramson et al. Ophthalmic intra-arterial infusion of melphalan has been successful in achieving effective tumor reduction with globe preservation in Reese-Ellsworth group Vb retinoblastoma cases in which other aggressive therapies have failed. It has been shown to be successful in achieving regression in all cases reported by Abramson et al, including enucleated eyes by histopathologic confirmation. This treatment approach is gaining popularity because it also minimizes serious systemic adverse effects including immunosuppression, need for blood transfusions, infections resulting in frequent hospitalizations, and secondary malignancies. At our institution, complications associated with this treatment include periocular inflammation, edema and injection, ophthalmic artery embolic events, vitreous hemorrhage, and tumor progression followed by enucleation. Herein, we report 3 cases of eyes that have undergone enucleation after treatment with the intra-arterial melphalan infusion (Table). To our knowledge, these are the first enucleated retinoblastoma cases documenting a viable tumor after supraselective intra-arterial melphalan infusion at our institution and among all published series to date. The Abramson et al group had no viable tumor on histopathologic examination of enucleated eyes.

All 3 cases had advanced tumors in which other aggressive treatment regimens had failed. Moreover, 2 of 3 cases had a viable tumor with high-risk characteristics for the development of metastatic disease on histopathologic evaluation. Two of 3 cases were undifferentiated tumors without rosette or fleurette formation. All 3 cases had tumors in the peripapillary location, with invasion of the optic nerve to the level or above the lamina cribrosa in 2 cases, but no tumor identified in the subarachnoid space. Vitreous seeding was identified in all 3 cases and minimal choroidal invasion, in 1 case. No anterior segment involvement or extraocular extension of the tumor was noted in any of the 3 cases.
On histopathological evaluation, 1 enucleated eye had a well-differentiated tumor. Poor tumor reduction with chemotherapy treatment for well-differentiated tumors has been previously reported.5 The other 2 enucleated eyes had high-grade histopathological characteristics based on pathological staging (pTNM), with risk of optic nerve invasion. These histopathologic findings confirmed that in certain cases enucleation remains definitive management to prevent local extension and metastasis.

In the Abramson et al study,3 intra-arterial melphalan treatment was shown to be successful in achieving regression in 7 cases. Four of 10 eyes had received prior therapy for retinoblastoma, and 3 of 4 eyes were successfully controlled with intra-arterial melphalan therapy. However, it is likely that the failure rate with intra-arterial melphalan therapy will be higher for tumors in which other aggressive chemotherapy has already failed. At our institution, the current “salvage” ratio for eyes undergoing this treatment for advanced primary or recurrent retinoblastoma is approximately 60%.4

In summary, ophthalmic intra-arterial infusion with melphalan is an alternative globe-conserving treatment option in advanced retinoblastoma cases. In certain patients, enucleation still remains the definitive treatment because a viable tumor can be seen histopathologically despite treatment with this novel approach.

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Figure 3. Patient 3, diagnosed with retinoblastoma (Reese-Ellsworth group Vb or International Classification of Retinoblastoma group D) (A), was treated with systemic chemoreduction and focal laser photocoagulation (B) and intra-arterial melphalan infusion (C). The eye was enucleated as the tumor progressed. Microscopic examination showed a viable, well-differentiated, exophytic (arrow) (D) (hematoxylin-eosin, original magnification ×100) retinal tumor with variable presence of fleurettes (asterisk) (E and F) (hematoxylin-eosin, original magnification ×400 [E] and 1000 [F]).

Table. Patients With Advanced Retinoblastoma Treated With Intra-arterial Melphalan and Who Subsequently Underwent Enucleation

<table>
<thead>
<tr>
<th>Patient No./Age at Dx, y</th>
<th>Laterality</th>
<th>Group</th>
<th>Previous Treatment</th>
<th>Age at First IAM, mo</th>
<th>Treated Eye(s)</th>
<th>Treatment Dose, mg</th>
<th>F/U Interval Since IAM, mo</th>
<th>Pathologic pTNM Stage</th>
<th>Differentiation</th>
<th>Viability, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/3 U</td>
<td>Vb D</td>
<td>Yes</td>
<td>OS</td>
<td>34</td>
<td>OS</td>
<td>3 and 7.5</td>
<td>6</td>
<td>pT2c</td>
<td>Undifferentiated</td>
<td>85</td>
</tr>
<tr>
<td>2/5 U</td>
<td>Vb D</td>
<td>Yes</td>
<td>OS</td>
<td>59</td>
<td>OS</td>
<td>5</td>
<td>5</td>
<td>pT2a</td>
<td>Undifferentiated</td>
<td>30</td>
</tr>
<tr>
<td>3/2 B</td>
<td>Vb D</td>
<td>Yes</td>
<td>OU</td>
<td>21</td>
<td>OD 5 and 7.5; OS 3</td>
<td>5</td>
<td>5</td>
<td>pT1</td>
<td>Differentiated</td>
<td>40</td>
</tr>
</tbody>
</table>

Abbreviations: B, bilateral retinoblastoma; Dx, diagnosis; F/U, follow-up; IAM, intra-arterial melphalan treatment; ICRB, International Classification of Retinoblastoma; R-E, Reese-Ellsworth; U, unilateral retinoblastoma.
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Correction

Errors in Table. In the Clinical Sciences article titled “Risks of Mortality, Myocardial Infarction, Bleeding, and Stroke Associated With Therapies for Age-Related Macular Degeneration” by Curtis et al, published in the October issue of the Archives (2010; 128[10]:1273-1279), there were errors in Table 4 on page 1277. The corrected table appears below.

Table 4. Unadjusted and Adjusted Outcomes at 1 Year for the Comparison of Ranibizumab Therapy vs Bevacizumab Therapy

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>No. of Adverse Events/No. (%) of Patients in the Treatment Group</th>
<th>Hazard Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ranibizumab</td>
<td>Bevacizumab</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>647/19 026 (4.1)</td>
<td>833/21 815 (4.7)</td>
</tr>
<tr>
<td>Incident myocardial infarction</td>
<td>170/19 026 (1.1)</td>
<td>227/21 815 (1.3)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>943/19 026 (5.8)</td>
<td>1017/21 815 (5.6)</td>
</tr>
<tr>
<td>Incident stroke</td>
<td>289/19 026 (1.8)</td>
<td>405/21 815 (2.2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exclusive Providers ⁵</th>
<th>Ranibizumab</th>
<th>Bevacizumab</th>
<th>Hazard Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>47/8421 (4.7)</td>
<td>225/6147 (4.3)</td>
<td>1.11 (0.87-1.43)</td>
</tr>
<tr>
<td>Incident myocardial infarction</td>
<td>68/421 (1.1)</td>
<td>69/6147 (1.3)</td>
<td>0.86 (0.53-1.41)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>225/8421 (5.3)</td>
<td>279/6147 (5.2)</td>
<td>1.02 (0.81-1.29)</td>
</tr>
<tr>
<td>Incident stroke</td>
<td>90/421 (2.1)</td>
<td>129/6147 (2.4)</td>
<td>0.80 (0.62-1.26)</td>
</tr>
</tbody>
</table>

⁎Hazard ratios for ranibizumab compared with bevacizumab after adjustment for the variables listed in Table 1.

bBy the end of the study period, almost all newly treated patients received ranibizumab or bevacizumab as first-line therapy. Therefore, in this secondary analysis, the study population was limited to newly treated patients who received ranibizumab or bevacizumab between July and December 2006.

cPatients with higher socioeconomic status may have been more likely to receive ranibizumab vs bevacizumab, so the primary analysis may have been subject to selection bias. Therefore, in this secondary analysis, the study population was limited to patients who received ranibizumab or bevacizumab in a medical practice that performed at least 20 injections and used a single drug in 95% or more of all intravitreous injections during the third or fourth quarter of 2006.