Periocular Topotecan for Intraocular Retinoblastoma

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Objective: To review the effectiveness and toxicity of periocular topotecan hydrochloride in fibrin sealant (Tis-see) for the control of intraocular retinoblastoma.

Methods: Retrospective medical record review of visually threatening or recurrent intraocular retinoblastoma treated with periocular topotecan.

Results: Eight children (10 eyes) received 1 to 4 injections of periocular topotecan in fibrin sealant, without or with concomitant laser and/or single freeze-thaw pre-chemotherapy cryotherapy. Median dose was 0.18 mg/kg (3.72 mg/m²). The 6 children who responded to treatment had small discrete tumors (8 International Intraocular Retinoblastoma Classification group A or B eyes). Of these, prior primary treatment for 3 children (3 eyes) was laser; for 1 child (2 eyes), systemic chemotherapy with focal laser; and for 2 children (3 eyes), periocular topotecan. In 4 children (4 eyes), tumor regression was sufficient for effective focal therapy, but in 2 children (4 eyes), long-term control required systemic chemotherapy. The 2 children who did not respond each had an International Intraocular Retinoblastoma Classification group D eye treated primarily with systemic chemotherapy, focal laser, and cryotherapy and recurrent disease that was not controlled by periocular topotecan; both eyes were eventually enucleated. No ocular and minimal hematological toxic effects were observed. At 11 months' median follow-up after topotecan treatment (18 months since diagnosis), all 8 group A and B eyes were retained with ongoing focal therapy required in only 1 group B eye; the 2 group D eyes were enucleated.

Conclusion: Periocular topotecan in fibrin sealant can achieve volume reduction of small and recurrent retinoblastoma sufficient to allow successful focal therapy.

for this cohort of patients and report evidence that per-ocular topotecan injection can induce tumor regression so that focal therapy can be successfully used to complete the cure of certain categories of retinoblastoma tumors.

**METHODS**

**DATA COLLECTION**

We conducted a retrospective medical record review of pa-tients with intraocular retinoblastoma treated with periocular topotecan injection at The Hospital for Sick Children from July 2008 to May 2009. Data collected included the International Intraocular Retinoblastoma Classification (IIRC) group of each eye and the American Joint Committee on Cancer staging of each child’s disease at diagnosis, the total number of injec-tions, therapies prior to and after the periocular injections, and outcome. Dose per kilogram (milligram per kilogram) of body weight was recorded, and dose per square meter (milligram per square meter) was calculated.

The tumor response to each topotecan injection was as-sessed qualitatively by comparing tumor size, consistency, and vascularization pattern, documented by serial RetCam (Clarity Medical Systems, Inc, Pleasanton, California) images and ultrasonography measurements. We recorded ocular toxic ef-fects and complete blood cell counts and differential counts weekly after each topotecan treatment to determine hemato-logical toxic effects. Toxic effects were graded according to the Common Terminology Criteria for Adverse Events version 3.0.14

Following injection, ocular mobility was tested at each exami-nation under anesthesia by forced duction test.1 Periocular to-potecan injection was deferred if the patients were neutrope-nic or thrombocytopenic on the pretreatment complete blood cell counts and differential counts.

**PERIOCULAR TOPOTECAN INJECTION PROTOCOL**

All topotecan injections were performed in the operating room, according to standard intraocular surgery protocol aseptic precautions. When injections were performed without a fibrin sealant (eg, the first injections for patients 1 and 6), 2.0 mg/m² of topotecan powder was diluted in sterile water. When performed with Tisseel fibrin sealant (Baxter, Deerfield, Illinois) (the remaining injections for patients 1 and 6; all injections for patients 2-5, 7, and 8), topotecan powder was dissolved in a thrombin and calcium chloride solution and mixed with the fibrin sealant just before injection (Figure 1). The final dose of topotecan hydrochloride for each injection ranged from 0.09 to 0.27 mg/kg (equivalent to 2.01-4.62 mg/m²), according to the protocol in the eAppendix (http://www.archophthalmol.com).

All injections were administered into the subtenon space. When Tisseel was used, the cannula-syringe setup was held in position for about 15 to 20 seconds after the injection to allow the fibrin sealant to clot (Figure 2). If there was leakage or spillage, the administered dose was estimated. Indirect oph-thalmoscopy was performed after each injection.

For patients requiring treatment of both eyes, only 1 eye was treated at alternating examinations under anesthesia to minimize potential systemic toxic effects, giving priority to the eye showing the most tumor activity and most likely to benefit. Serial subtenon injections were given into different quadrants.

**STATISTICS**

We used descriptive statistical methods to analyze the data, cal-culating the means, medians, and proportions of each data set.

**PATIENT DEMOGRAPHICS**

Ten eyes from 8 patients were treated with periocular to-potecan (Table 1). At presentation, 1 eye (patient 1) was classified as IIRC group A (TNM stage T1aN0M0); 2 eyes in 2 patients and 1 eye in 3 patients (patients 2-6) as group B (T1bN0M0); and 2 eyes (patients 7 and 8) as group D (T2bN0M0). Six children (patients 1, 2, and 5-8) had bilateral retinoblastoma (patients 1, 5, and 6 with family history). Both eyes (IIRC group B) of patients 5 and 6 and the worse-tumor eye of patients 1, 2, 7, and 8 were treated with topotecan.

Three eyes in 2 children (patients 3 and 5) had small-volume tumors and had no other treatment before peri-ocular topotecan injection. Three eyes in 3 children (pa-tients 1, 2, and 4) had prior focal therapy (laser and cryotherapy). Patient 6 had prior chemotherapy (2-
cycle standard-dose carboplatin/high-dose etoposide/standard-dose vincristine without high-dose cyclosporine, instead of the Toronto Protocol [high-dose carboplatin/high-dose etoposide/standard-dose vincristine with high-dose cyclosporine to circumvent the multidrug resistance P-glycoprotein], because she was a baby with immature renal function), and both eyes had prior focal therapy. Two patients had recurrent American Joint Committee on Cancer stage T2b disease in their worse-tumor eye, with persistent small-volume recurrences despite the Toronto Protocol\(^{15}\) (patient 7: 8 cycles; patient 8: 6 cycles), laser, and cryotherapy; patient 7 also had stereotactic irradiation for the worse-tumor but better-vision eye (Table 2).

## RATIONALE FOR PERIOCULAR TOPOTECAN

Eight eyes (patients 1–6) had small-volume tumors (IIRC group A, 1 eye; group B, 7 eyes) (Table 1). Bilateral disease was present in 4 children (6 eyes), in whom only their worse group B eyes received topotecan injections (Table 3). The central tumors in both eyes of patient 6 were treated with topotecan to reduce the amount of central vision–compromising focal laser therapy needed. Four children (patients 1, 2, 5, and 6) with 6 involved eyes were premature or full-term neonates who were too small (weights, 2.6–8.8 kg), with still immature renal function (Table 3), for the Toronto Protocol's renotoxic high-dose cyclosporine and high-dose carboplatin. We avoided

### Table 1. Patient Demographics at Diagnosis

<table>
<thead>
<tr>
<th>Patient/Age, mo</th>
<th>Family History</th>
<th>Bilateral Disease</th>
<th>IIRC Group</th>
<th>TNM* Stage</th>
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<tbody>
<tr>
<td>1/1</td>
<td>Y</td>
<td>Y</td>
<td>A</td>
<td>T1aN0M0</td>
</tr>
<tr>
<td>2/2</td>
<td>N</td>
<td>Y</td>
<td>B</td>
<td>T1aN0M0</td>
</tr>
<tr>
<td>3/16</td>
<td>N</td>
<td>N</td>
<td>B</td>
<td>T1bN0M0</td>
</tr>
<tr>
<td>4/53</td>
<td>N</td>
<td>N</td>
<td>B</td>
<td>T1bN0M0</td>
</tr>
<tr>
<td>5/0.1</td>
<td>Y</td>
<td>Y</td>
<td>B, B</td>
<td>T1bN0M0</td>
</tr>
<tr>
<td>6/3</td>
<td>Y</td>
<td>Y</td>
<td>B, B</td>
<td>T1bN0M0</td>
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<tr>
<td>7/21</td>
<td>N</td>
<td>Y</td>
<td>D</td>
<td>T2bN0M0</td>
</tr>
<tr>
<td>8/12</td>
<td>N</td>
<td>Y</td>
<td>D</td>
<td>T2bN0M0</td>
</tr>
</tbody>
</table>

Abbreviations: IIRC, International Intraocular Retinoblastoma Classification.\(^{12}\)  
*a American Joint Committee on Cancer classification.\(^{13}\)

### Table 2. Details of Therapy Provided Prior and Subsequent to Periocular Topotecan Injection, Indication for Injection, Tumor Status, and Follow-up Duration

<table>
<thead>
<tr>
<th>Patient/Eye</th>
<th>Primary Indication for Injection</th>
<th>Previous Therapy</th>
<th>Overall Response to Topotecan</th>
<th>Eye Outcome</th>
<th>Follow-up From Dx, mo</th>
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</thead>
<tbody>
<tr>
<td>1/R</td>
<td>Recurrent tumor not controlled by Fo</td>
<td>Fo</td>
<td>Better</td>
<td>Inactive</td>
<td>18</td>
</tr>
<tr>
<td>2/L</td>
<td>Recurrent tumor not controlled by Fo</td>
<td>Fo</td>
<td>Better</td>
<td>Inactive</td>
<td>30</td>
</tr>
<tr>
<td>3/R</td>
<td>Avoid systemic chemotherapy or Enuc</td>
<td>None</td>
<td>Better</td>
<td>Inactive</td>
<td>19</td>
</tr>
<tr>
<td>4/L</td>
<td>Avoid systemic chemotherapy or Enuc</td>
<td>Fo</td>
<td>Better</td>
<td>Inactive</td>
<td>16</td>
</tr>
<tr>
<td>5/R</td>
<td>GFR not adequate for systemic chemotherapy</td>
<td>None</td>
<td>Worse</td>
<td>Active</td>
<td>18</td>
</tr>
<tr>
<td>5/L</td>
<td>GFR not adequate for systemic chemotherapy</td>
<td>None</td>
<td>Worse</td>
<td>Inactive</td>
<td>18</td>
</tr>
<tr>
<td>6/R</td>
<td>GFR not adequate for systemic chemotherapy</td>
<td>Fo; Ch(2)</td>
<td>Worse</td>
<td>Inactive</td>
<td>26</td>
</tr>
<tr>
<td>6/L</td>
<td>GFR not adequate for systemic chemotherapy</td>
<td>Fo; Ch(2)</td>
<td>Worse</td>
<td>Inactive</td>
<td>26</td>
</tr>
<tr>
<td>7/L</td>
<td>Recurrent tumor</td>
<td>Ch(6); Fo; Ch(2); Fo; Ch(2); Rad</td>
<td>Worse</td>
<td>Fo; Enuc</td>
<td>58</td>
</tr>
<tr>
<td>8/L</td>
<td>Recurrent tumor</td>
<td>Ch(4); Fo; Ch(2)</td>
<td>Worse</td>
<td>Fo; Enuc</td>
<td>30</td>
</tr>
</tbody>
</table>

Total Mean, 17  Median, 16  Mean, 26  Median, 22

Abbreviations: Ch, chemotherapy (number of cycles); Dx, diagnosis; Enuc, enucleation; Fo, focal therapy; GFR, glomerular filtration rate; Rad, stereotactic external beam irradiation.

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noncyclosporine protocols that might induce further expression of the multidrug resistance P-glycoprotein, a risk that outweighed the temporary benefit of tumor shrinkage. Topotecan is a drug that is less susceptible to multidrug resistance. Likewise, we avoided low- or standard-dose carboplatin, which is less effective than high-dose carboplatin for shrinking retinoblastoma tumors but may induce further drug resistance. For patients 3 and 4 with unilateral retinoblastoma and potentially salvageable central vision, we used periocular topotecan to avoid systemic chemotherapy. We avoided brachytherapy because it is not precise enough to avoid damage to the macula in such patients and its long-term ocular complications are significant. Each injection cost CaD $892.68 (US $927.32) (eTable).

Patients 7 and 8 with bilateral retinoblastoma had advanced IIRC group D disease in 1 of their 2 eyes at diagnosis and small-volume systemic chemotherapy-resistant recurrences (Table 1), so periocular topotecan was given to try and avoid enucleation (Table 3).

**TOPOTECAN TREATMENTS**

In total, 28 subtenon topotecan injections were performed, 26 with and 2 without fibrin sealant (Table 3). Each treated eye received 1 to 4 subtenon topotecan injections, with a mean interval of 23 days between injections.

Single freeze-thaw “prechemotherapy” cryotherapy in the normal peripheral retina induced a serous effusion that temporarily breached the blood-eye barrier to significantly increase intraocular drug penetration. Likewise, we avoided low- or standard-dose carboplatin, which is less effective than high-dose carboplatin for shrinking retinoblastoma tumors but may induce further drug resistance. For patients 3 and 4 with unilateral retinoblastoma and potentially salvageable central vision, we used periocular topotecan to avoid systemic chemotherapy. We avoided brachytherapy because it is not precise enough to avoid damage to the macula in such patients and its long-term ocular complications are significant. Each injection cost CaD $892.68 (US $927.32) (eTable).

**Table 3. Topotecan Injection Details**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Event/Eye</th>
<th>Fibrin Sealant</th>
<th>Weight, kg</th>
<th>Dose mg/kg</th>
<th>Topotecan, mg/mL</th>
<th>Prechemo Cryotherapy</th>
<th>Focal Therapy</th>
<th>Time, d</th>
<th>Tumor Outcome</th>
<th>Ocular Toxic Effect</th>
<th>CTCAE Grade</th>
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</thead>
<tbody>
<tr>
<td>1/R</td>
<td>Y</td>
<td>5.8</td>
<td>0.21</td>
<td>3.75</td>
<td>2.4</td>
<td>Y</td>
<td>Y</td>
<td>14</td>
<td>Better</td>
<td>Red eye</td>
<td>2 (ANC)</td>
</tr>
<tr>
<td>2/R</td>
<td>Y</td>
<td>6.1</td>
<td>0.2</td>
<td>3.64</td>
<td>2</td>
<td>Y</td>
<td>Y</td>
<td>16</td>
<td>Better</td>
<td>None</td>
<td>3 (ANC)</td>
</tr>
<tr>
<td>3/R</td>
<td>Y</td>
<td>6.1</td>
<td>0.21</td>
<td>3.7</td>
<td>2.14</td>
<td>N</td>
<td>Y</td>
<td>14</td>
<td>Better</td>
<td>None</td>
<td>3 (ANC)</td>
</tr>
<tr>
<td>4/R</td>
<td>Y</td>
<td>6.1</td>
<td>0.21</td>
<td>3.74</td>
<td>2.14</td>
<td>N</td>
<td>Y</td>
<td>14</td>
<td>Same</td>
<td>None</td>
<td>3 (ANC)</td>
</tr>
<tr>
<td>1/L</td>
<td>N</td>
<td>5.8</td>
<td>0.5</td>
<td>0.09</td>
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<td>NA</td>
<td>Y</td>
<td>26</td>
<td>Better</td>
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<td>None</td>
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<tr>
<td>2/L</td>
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<td>6.1</td>
<td>0.16</td>
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<td>Y</td>
<td>N</td>
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<td>None</td>
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<tr>
<td>3/L</td>
<td>Y</td>
<td>6.1</td>
<td>0.16</td>
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<td>NA</td>
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<td>Y</td>
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<tr>
<td>4/L</td>
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<td>6.6</td>
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<td>3.71</td>
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<td>N</td>
<td>N</td>
<td>47</td>
<td>Same</td>
<td>None</td>
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</tr>
<tr>
<td>1/R</td>
<td>Y</td>
<td>13.0</td>
<td>2</td>
<td>0.15</td>
<td>3.7</td>
<td>Y</td>
<td>N</td>
<td>19</td>
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<td>None</td>
<td>3 (ANC)</td>
</tr>
<tr>
<td>2/R</td>
<td>Y</td>
<td>13.2</td>
<td>2.57</td>
<td>0.19</td>
<td>4.62</td>
<td>2.43</td>
<td>Y</td>
<td>28</td>
<td>Better</td>
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<td>0</td>
</tr>
<tr>
<td>3/R</td>
<td>Y</td>
<td>12.6</td>
<td>2.05</td>
<td>0.16</td>
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<td>Y</td>
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<tr>
<td>4/R</td>
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<td>2.12</td>
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<td>3.76</td>
<td>3.21</td>
<td>Y</td>
<td>12</td>
<td>Better</td>
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<td>Better</td>
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</tr>
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<td>1.52</td>
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<td>2.05</td>
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<td>Y</td>
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<td>Better</td>
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<td>None</td>
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<tr>
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<td>3.78</td>
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<td>0.18</td>
<td>3.76</td>
<td>3.78</td>
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<td>Worse</td>
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<tr>
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<td>2.27</td>
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<td>1.74</td>
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<td>19</td>
<td>Worse</td>
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<td>3 (ANC)</td>
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<td>1.74</td>
<td>0.18</td>
<td>3.76</td>
<td>3.78</td>
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<td>19</td>
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<tr>
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<td>3.15</td>
<td>N</td>
<td>23</td>
<td>Worse</td>
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</tbody>
</table>

Abbreviations: ANC, low absolute neutrophil count; CTCAE, Common Terminology Criteria for Adverse Events; Hb, low hemoglobin level; NA, data not available; Plt, low platelet count; Prechemo, prechemotherapy; WBC, low white blood cell count.

Topotecan given as topotecan hydrochloride.
Of the 8 eyes (patients 1-6) with small-volume tumors, 4 (50%) (patients 1-4) improved after periocular topotecan injection (Table 2 and Table 3 and Figure 3A). The 4 eyes that did not improve were in the 2 bilaterally affected children (patients 5 and 6), each with both eyes at visual risk treated with topotecan (Table 2 and Table 3 and Figure 3B). These 2 children had longer intervals between the topotecan delivered to each eye, because only 1 eye was treated at each examination under anesthesia, effectively reducing the treatment dose intensity. Topotecan doses for the 4 eyes that responded were not different from those of the 4 eyes that did not respond.

Response to topotecan was most impressive in patients 1 to 3. Patient 1 had a 2-mm-thick, 3- to 4-mm-diameter right eye tumor near the superior arcade that did not respond to laser therapy alone. The tumor responded to the first topotecan treatment; there were no significant toxic effects from the total 4 topotecan injections. No active disease was evident at 15 months after completing topotecan treatment. Patient 2, in the eye staged group B at diagnosis, later developed multiple large vitreous seeds that had spread from a superonasal tumor to lie near the optic nerve and macula (Figure 3A). She had a large chromosome 13 deletion, was small for...
age and hypotonic, had aspiration and swallowing problems, and was dependent on jejunal-tube feeding. She was not a candidate for systemic chemotherapy. The seeds responded to the first topotecan treatment and she had no significant toxic effects from 4 topotecan treatments. No active disease was evident at 16 months after completing topotecan treatment. Patient 3 had unilateral macular retinoblastoma against the temporal side of the optic nerve, 3.1 mm thick and 10.5 mm wide (Figure 3A). This was judged too large for focal therapy without systemic chemotherapy, but the other eye was normal. After the first topotecan injection, there was a subtle shrinkage in the horizontal dimensions of the tumor, but after 4 treatments, the tumor was markedly flatter and smaller. Repeated laser therapy using 532-nm and 810-nm lasers was started after the fourth topotecan dose and resulted in a flat, inactive scar, 15 months after completing topotecan.

**Eyes With Multiply Recurrent Disease**

In both patients with group D eyes who developed multiply recurrent retinoblastoma after extensive treatment (patients 7 and 8), the tumors did not respond but continued to grow. Patient 7 had more focal therapy and then enucleation, and patient 8 had more systemic chemotherapy without response so the eye was enucleated.

**OCULAR AND SYSTEMIC TOXIC EFFECTS**

The mean follow-up was 17 months after completing topotecan injection and 26 months after diagnosis (Table 2). Ocular adverse effects of the topotecan injections were minimal. One episode of conjunctival congestion (patient 3) responded to topical corticosteroids. Eyelid chemosis in patient 8 after topotecan was given with triple freeze-thaw cryotherapy improved without intervention (Table 3). No ocular motility restriction was noted, unlike the 100% motility restriction observed after our prior use of subtenon carboplatin. We did not determine whether the absence of ocular motility restriction was due to the use of topotecan rather than carboplatin or the use of fibrin sealant, which may have reduced drug diffusion throughout the orbit, leading to fewer complications.

Hematological toxic effects included low hemoglobin level and absolute neutrophil, white blood cell, and platelet counts (Table 3), which recovered spontaneously. Hematological toxic effects were absent in 1 patient (who received only 1 injection) and mild in 6 patients (Common Terminology Criteria for Adverse Events grades 1–3). Two patients showed grade 4 hematological toxic effects after a series of topotecan hydrochloride injections with dosages at the high end (0.2 and 0.27 mg/kg [3.71 and 3.76 mg/m²]). Blood cell counts improved after 1 week, normalized in 2 weeks, and never required intervention.

**COMMENT**

To our knowledge, we report the first successful use of periocular topotecan for small-volume, visually threatening retinoblastoma in young infants, some with familial retinoblastoma. Young, sometimes premature, infants who have small tumors detected early because of RB1 mutation testing in familial cases undergo early and frequent surveillance by examination under anesthesia. These young children are difficult to treat with conventional chemotherapy, as their immature kidneys cannot effectively clear high-dose systemic carboplatin and cyclosporine. Focal therapy for small tumors is potentially curative but may be contraindicated if the tumor is adjacent to the macula or optic nerve where focal therapy will destroy central vision. We now show that small-volume tumors can be successfully treated by periocular topotecan, sometimes avoiding the more toxic systemic chemotherapy.

Periocular chemotherapy has been explored previously as a method to minimize systemic exposure to chemotherapy in the treatment of intraocular retinoblastoma and suggested as a strategy to deliver chemotherapy to the vitreous. Transscleral diffusion of a hydrophilic compound, such as topotecan, occurs through the interfibrillar aqueous media of gel-like proteoglycans, not cellular membranes. Factors that can influence the permeability of the human sclera include molecular size and radius of the solute, with small molecular radius being a better predictor of permeability than low molecular weight, and the thickness of the sclera, which is thinnest (0.39 mm [SD, 0.17 mm]) at the equator. The thickness of the sclera might be of significance for large molecules like topotecan. Age, cryotherapy, and diode laser treatment do not alter scleral permeability or ultrastructure.

Chemotherapy agents investigated for transscleral delivery include methotrexate, cisplatin, carboplatin, paclitaxel, etoposide, and topotecan. To our knowledge, only carboplatin and topotecan have been used for transscleral treatment of retinoblastoma. Subconjunctival carboplatin injections evaluated in human and animal studies suggested possible response in intraocular retinoblastoma. However, reported local toxic effects include restriction of ocular motility, orbital fibrosis making subsequent enucleation more difficult and at risk for globe rupture, and optic nerve atrophy and blindness.

The use of a fibrin clot to deliver transscleral carboplatin was demonstrated in rabbits in an attempt to improve intraocular drug concentrations. Fibrin sealant is a Food and Drug Administration–approved, human protein–derived surgical adhesive that can serve as a biodegradable, semisolid medium for transscleral drug delivery. Delivery of carboplatin in fibrin sealant has been investigated for its potential to provide sustained therapeutic concentrations over a longer duration in the target tissue than non–fibrin sealant techniques. In rabbits, injections of carboplatin in fibrin sealant had no associated periocular fibrosis. In LHβ-TAg retinoblastoma transgenic mice, subconjunctival administration of topotecan in fibrin sealant created a drug depot sufficient for sustained drug delivery up to 3 weeks after injection. By placing the fibrin clot permeated with topotecan next to the sclera, as in our study, we presumably maximize drug exposure, extend the duration of thera-
peutically significant intraocular drug penetration, and reduce the need for repeated periocular injections, since each injection is associated with a potential risk for globe perforation and thus tumor dissemination. However, this was effective for eyes with small-volume tumors, not those with complicated recurrent disease.

Topotecan is a hydrophilic compound that is excreted mainly through the kidneys and to a lesser extent by the liver. When given systemically, it does not require dose adjustment for liver dysfunction. Severe renal dysfunction does impair drug clearance of topotecan, but topotecan has no urothelial toxicity. The dose-limiting adverse effect of systemic administration is neutropenia and thrombocytopenia occurring between days 8 and day 15. This is reversible and requires no intervention. In our experience, hematologic toxic effects are most common in premature infants and young babies and in patients with heavy pretreatment with systemic chemotherapy. Topotecan and carboplatin were found to have a synergistic effect against retinoblastoma growth in rodent models, but in a phase 1 study of the combination in pediatric solid tumors, significant hematological toxic effects were observed even with cytokine granulocyte colony-stimulating factor support. Therefore, periocular topotecan injections in our patients were not performed concomitantly with carboplatin-based or other systemic chemotherapy.

We used 3.75 mg/m² of topotecan hydrochloride as a single dose approximately every 3 weeks in the moderate-dose range for single-agent systemic topotecan for 3-weekly, 5-day systemic therapy. High-dose 3-weekly, 5-day systemic single-agent therapy at 10 mg/m² has been used to treat extraocular and relapsed/refractory intraocular retinoblastoma, with severe hematological toxic effects despite granulocyte colony-stimulating factor support. Therefore, systemic topotecan causes known hematological toxic effects when given at the dosages that were administered periocularly in our study, yet we observed only grade 1 to 3 hematological toxic effects in 6 patients and grade 4 hematological toxic effects in 2 patients (Table 3). All adverse effects resolved without intervention. Other known toxic effects of systemic topotecan, including alopecia and gastrointestinal effects, were not observed in our patients.

The low toxicity observed supports this method of topotecan administration resulted in low and slow systemic absorption. Animal studies of periocular administration of topotecan showed systemic absorption of the drug, which could be detected in the vitreous of the non-injected contralateral eye. However, in a phase 1 trial, systemic drug levels from periocular topotecan were lower than from intravenous administration of a similar dose in the same patients and resulted in lower systemic toxic effects. The rather modest systemic toxic effects we and others have encountered suggests that the maximum-tolerated dose of periocular topotecan in fibrin sealant has not been reached. A clinical trial with dose escalation is warranted to define the maximum-tolerated dose, which would likely have the maximum efficacy for treatment of intraocular retinoblastoma.

The low and slow systemic absorption of topotecan is likely due to the effect of the fibrin binding to the drug keeping it in the periocular region. This causes a high local drug concentration and increases transscleral drug concentration. The delay to reach the bone marrow may also decrease the activity of the drug. The therapeutic concentration of a topically applied drug is dependent on the levels achieved in intraocular tissues. In each of the cases we report, the maximum topotecan hydrochloride concentration delivered was 3.78 mg/mL, made feasible by the small volume in which the drug was dissolved. In this small preliminary study, we were unable to correlate response with topotecan dosage administered. However, periocular topotecan appeared to work better with chemotherapy-naive, small-volume tumors, even with vitreous seeding.

Our results suggest that high-dose periocular topotecan in fibrin sealant can be safe and effective in the treatment of small-volume intraocular retinoblastoma, even with vitreous seeding. Periocular injection of topotecan has fewer ocular toxic effects than periocular carboplatin. Systemic toxic effects were negligible at a toptecan hydrochloride dosage up to 3.75 mg/m². Further animal and clinical trials are warranted to understand the mechanisms better and for assessment of maximum-tolerated dosages at which periocular topotecan with fibrin sealant may be used to manage intraocular retinoblastoma. Therefore, we propose a prospective dose-escalation study of periocular topotecan for managing small-volume retinoblastoma that has been exposed to minimal or prior chemotherapy treatment.

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Online-Only Material: The eAppendix and eTable are available at http://www.archophthalmol.com.

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