A Phase I Study of Periocular Topotecan in Children with Intraocular Retinoblastoma

Guillermo L. Chantada,1 Adriana C. Fandino,2 Angel M. Carcaboso,3 Eduardo Lagomarsino,4 Maria T. G. de Davila,5 Myriam R. Guitter,1 Adriana B. Rose,1 Julio Manzitti,2 Guillermo F. Bramuglia,5 and David H. Abramson6

PURPOSE. To identify the maximum tolerated dose and dose-limiting toxicity of periocular topotecan in patients with relapsed or resistant intraocular retinoblastoma who are facing imminent enucleation.

METHODS. For this phase I study, a starting dose of 0.5 mg of periocular topotecan administered through a 25-gauge needle was given with intrapatient escalation at a rate of 0.5 mg/cycle according to toxicity, up to a maximum dose of 2 mg. Two courses separated by 2 weeks were scheduled. Plasma levels of topotecan were measured by high-performance liquid chromatography in patients with available intraocular catheters.

RESULTS. Seven eyes of five patients were treated with a total of 14 courses of periocular topotecan. Only mild orbital edema occurred, and grade 1 vomiting developed in the first patient that was controlled with ondansetron for the following courses. Dose-limiting toxicity was not reached and the maximum tolerated dose was set at the target dose of 2 mg (n = 5 eyes). Lactone topotecan systemic exposure was lower than 55 ng/mL • h and it correlated linearly with dose in this small cohort. Even though the study was not designed to assess response, one eye was preserved after a partial response, but the remaining six were enucleated, either after a short period of disease stabilization followed by further therapy with other agents in five patients or by rapidly progressive disease in one.

CONCLUSIONS. The dose limiting toxicity was not reached. Up to 2 mg of periocular topotecan could be given safely, but further studies are necessary to determine its effect on retinoblastoma (ClinicalTrials.gov number, NCT00460876). (Invest Ophtalmol Vis Sci. 2009;50:1492–1496) DOI:10.1167/iovs.08-2737

Retinoblastoma is the most common primary intraocular malignancy in childhood. It is an uncommon tumor occurring in 27/1,000,000 infants in the United States. More than 90% of the affected patients survive with current therapy, and most efforts are now concentrated in increasing the eye preservation rate. Systemic chemoreduction of intraocular tumors with carboplatin, usually associated with etoposide and vincristine, followed by local therapy has become the standard conservative treatment for intraocular retinoblastoma worldwide. This treatment leads to a reduction or a delay in the use of external beam radiotherapy, with the purpose of decreasing irradiation-induced secondary neoplasms. The results of chemoreduction are more encouraging in eyes with less advanced disease; however, eyes with extensive vitreous seeding have a worse prognosis, even when external beam radiation is added. Poor penetration of systematically delivered chemotherapy drugs into the avascular vitreous may be a major reason for treatment failure. To overcome this limitation, clinicians may choose to intensify systemic chemotherapy, but such an increase could lead to significant systemic toxicities in both the short and long term, including fatal secondary leukemia. Another alternative would be to explore local routes for drug delivery in an attempt to increase the chemotheraphy concentration in the eye while reducing the systemic exposure.

Periocular chemotherapy (subconjunctival, subtenon, and retrobulbar) is being explored as a way of minimizing the systemic exposure to chemotherapeutic drugs in the treatment of intraocular retinoblastoma. However, only carboplatin has been widely used in children with retinoblastoma by this route. Although virtually devoid of systemic toxicity, it can cause severe local adverse effects including orbital fibrosis and atrophy of the optic nerve. Therefore, the identification of new drugs or new delivery systems suitable for periocular use is necessary.

Topotecan is active against a variety of pediatric tumors, including retinoblastoma. Our group and others reported its preliminary activity in selected patients with retinoblastoma after intravenous treatment. In addition, animal data suggest that the combination of topotecan and carboplatin has a synergistic effect. The ocular pharmacokinetics of topotecan has been studied recently, showing a good penetration of the vitreous after intraocular injection. Our group found potentially active topotecan levels in the vitreous after periocular administration. However, in that animal study, we found that a significant amount of periocularly administered topotecan was absorbed from the injection site, reaching the systemic circulation. Therefore, we decided to evaluate its plasma levels in children included in this study as an additional tool for evaluating potential systemic toxicity.

Therefore, the objectives of this phase I study were (1) to determine the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) of periocular topotecan; (2) to evaluate the toxicity profile of periocular topotecan; and (3) to describe the plasma pharmacokinetics of total and lactone topotecan after different dosages of periocular topotecan.
**Methods**

**Patients**

Patients with Reese-Ellsworth Group Vb (International ABC classification group D) retinoblastoma that relapsed or was resistant after standard treatment including chemoreduction with at least four courses of carboplatin, etoposide, and vincristine and local treatments such as cryotherapy, laser therapy or brachytherapy and external beam radiotherapy and facing imminent enucleation were eligible. Patients with International Retinoblastoma Staging System (IRSS) stage 2 or greater were not eligible. A minimum of 4 weeks’ washout interval after prior treatments was necessary and eligible patients had to have recovered from all toxicities to enter the study.

Before study entry, all patients had a full medical history, physical examination, and ophthalmic evaluation under anesthesia, brain, and orbital contrast-enhanced computed tomography (CT) or magnetic resonance image (MRI) scans and complete blood cell count and biochemical profile. Normal values for blood cell counts and liver and renal function tests were required for study entry.

This research adhered to the tenets of the Declaration of Helsinki and institutional review board approval as well as authorization by the local regulatory agency for clinical trials (ANMAT) were obtained. Written informed consent was obtained from parents or guardians.

**Drug Administration**

Topotecan was administered with a 25-gauge needle periorcularly in the affected eye, usually at the superior temporal quadrant under general anesthesia. We use the term periorcular as a generic term, instead of subtenon to account for the potential discrepancies in the distribution of high volumes of the drug in the periorcular space. Topotecan (commercially available as Hyacam; Glaxo Smith-Kline, Buenos Aires, Argentina) was diluted with saline under a vertical laminar airflow hood to a final concentration of 1 mg/mL and administered just after reconstitution. Concentration was chosen as the highest stable dilution recommended by the manufacturer and was the one tested in our animal model. No other topical or systemic medication was allowed for the first 24 hours, except for ondansetron to manage nausea and vomiting. Patients were usually admitted overnight and monitored closely for toxicity.

**Toxicity Evaluation**

A baseline ophthalmic evaluation was performed at entry and daily for the first 2 days and weekly thereafter. Toxicity was graded according to the National Cancer Institute’s Common Terminology Criteria for Adverse Events (CTCAE, ver. 3.0 http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaeV3to2.pdf, provided in the public domain by the National Cancer Institute, Bethesda, MD). Local toxicity evaluation included weekly clinical and funduscopic examination. Examinations under anesthesia and by slit lamp were performed every 2 weeks. Any systemic grade 4 toxicity induced by periorcular topotecan was considered dose-limiting, as well as ocular toxicities that required surgical management (grade 3 or higher) and scleral necrosis with grade 2 or higher scores.

Patients were monitored on a weekly basis by a pediatric oncologist and laboratory evaluation of hematologic, liver, and renal functions were performed at each visit. Enucleation of affected eyes was indicated when tumor progression no longer controllable with conservative measures was evident. After enucleation, all eyes were thoroughly examined by a pathologist (MTGD) looking for disease extension and evidence of toxicity.

**Study Design**

For this phase I study, the starting dose was 0.5 mg. Since this treatment was considered local therapy and minimal toxicity was anticipated, intrapatient escalation at a rate of 0.5 mg/cycle was scheduled. Patients were scheduled to receive two courses of periorcular topotecan. All had massive intraocular tumors and vitreous seeding. Patients’ characteristics and outcome are summarized in Table 1.
Toxicity

No patient experienced DLT. Periocular topotecan was well tolerated in all patients. Common but not dose-limiting toxicities included mild orbital edema and nausea. Orbital edema occurred in six eyes, but resolved spontaneously within 24 hours of the application of topotecan. Two patients had residual periorbital erythema (both received a 2-mg dose) that persisted for a few weeks and resolved slowly thereafter. The first patient included in the study had grade 1 vomiting that persisted for a few weeks and resolved slowly thereafter. One patient had rapidly progressive disease, received no poststudy conservative treatment and underwent enucleation 20 days after the second course of periocular topotecan. There was disease stabilization in five treated eyes. Two of them received further systemic chemoreduction with intravenous topotecan alone or with cyclophosphamide, but their eyes had to be removed because of progressive disease during follow-up. Two patients (three eyes) received additional local therapy and no further chemotherapy. Two eyes were enucleated and the remaining one had a partial response to periocular topotecan and is still preserved after an 8 month follow-up. Therefore, six of seven treated eyes have been enucleated thus far.

Pharmacokinetic Studies

We obtained plasma levels in six courses of four patients belonging to every dose level, and the calculated topotecan lactone plasma exposures are shown in Table 3. One patient who had received 0.5 mg of periocular topotecan, also received subsequently a 0.5-mg dose intravenously together with cyclophosphamide. In that patient, the calculated topotecan lactone AUC was 23.9 ng/mL h for the intravenous and 12.71 ng/mL h for the periocular route. After periocular administration, topotecan lactone systemic exposure (AUC) increased linearly with dose ($r^2 = 0.98, P = 0.003$). The calculated mean concentration–time profile of lactone topotecan is displayed in Figure 1.

Poststudy Treatment

One patient had rapidly progressive disease, received no poststudy conservative treatment and underwent enucleation 20 days after the second course of periocular topotecan. There was disease stabilization in five treated eyes. Two of them received further systemic chemoreduction with intravenous topotecan alone or with cyclophosphamide, but their eyes had to be removed because of progressive disease during follow-up. Two patients (three eyes) received additional local therapy and no further chemotherapy. Two eyes were enucleated and the remaining one had a partial response to periocular topotecan and is still preserved after an 8 month follow-up. Therefore, six of seven treated eyes have been enucleated thus far.

Table 2. Laboratory Values at the Time of Accrual and after One (2 Weeks) and Two (at 4 Weeks) Courses of Periocular Topotecan

<table>
<thead>
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<th>On Accrual</th>
<th>At 2 Weeks</th>
<th>At 4 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cells (mm$^3$)</td>
<td>8,700 (4,300–10,770)</td>
<td>7,600 (7,400–9,400)</td>
<td>7,600 (4,000–10,100)</td>
</tr>
<tr>
<td>Absolute neutrophil count</td>
<td>2,400 (1,500–5,000)</td>
<td>2,691 (1,200–4,000)</td>
<td>2,500 (1,800–6,000)</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>11.9 (10.5–12)</td>
<td>11.9 (10.5–12.7)</td>
<td>11.9 (10.1–13.6)</td>
</tr>
<tr>
<td>Platelet count (mm$^3$)</td>
<td>408,000 (211,000–461,000)</td>
<td>283,000 (273,000–289,000)</td>
<td>283,000 (189,000–450,000)</td>
</tr>
<tr>
<td>SGOT (UI/L)</td>
<td>26 (16–42)</td>
<td>27 (17–34)</td>
<td>29 (27–33)</td>
</tr>
<tr>
<td>SGPT (UI/L)</td>
<td>26 (17–42)</td>
<td>27 (17–34)</td>
<td>15 (10–26)</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.39 (0.28–0.48)</td>
<td>0.36 (0.29–0.48)</td>
<td>0.43 (0.31–0.56)</td>
</tr>
</tbody>
</table>

Data are shown as the median and upper and lower range. There were no significant differences among groups.
few other phase I studies for intraocular retinoblastoma and particular situation in retinoblastoma. Moreover, there are we are not aware of a specific trial design that considers this tic doses in the lower-dose cohorts for other malignancies, but been recently proposed to limit the exposure to subtherapeu- case it occurred, even when it would not qualify for DLT, we expected that severe toxicity from this treatment would occur enucleation. This possibility posed an ethical challenge for the hence, participants in this study were potentially at risk for eyes may lead to potentially fatal extraocular dissemination. To our knowledge, no other drug besides carboplatin has been widely used periocularly in children with retinoblastoma. Therefore, our study may add significant information of a new treatment modality for the treatment of this malignancy.

The design for this phase I trial posed a significant chal- lene. Because of its high curability, a phase I study would be justified only in patients with advanced intraocular disease facing imminent enucleation after failing standard conservative treatments. However, prolonged attempts to preserve these eyes may lead to potentially fatal extraocular dissemination. Therefore, participants in this study were potentially at risk for this fatal complication, which could be avoided by timely enucleation. This possibility posed an ethical challenge for the design of the study, since a relatively large cohort would be needed for a precise estimation of MTD in case the study was done after traditional guidelines for dose escalation. Traditional phase I studies are usually designed to detect severe toxicity in a timely fashion, but the response rate is usually lower than 10% because of the inclusion of heavily pretreated patients. Therefore, we also anticipated a low response rate for our study. According to previous data on the use of periocular carboplatin and our animal study of periocular topotecan, we expected that severe toxicity from this treatment would occur infrequently. Therefore, we designed this study allowing for inpatient escalation if no moderate toxicity occurred. In case it occurred, even when it would not qualify for DLT, we would switch to a standard design with three patients per level and no inpatient escalation, to better estimate the MTD. Trial designs allowing for rapid inpatient escalation have been recently proposed to limit the exposure to subtherapeutic doses in the lower-dose cohorts for other malignancies, but we are not aware of a specific trial design that considers this particular situation in retinoblastoma. Moreover, there are few other phase I studies for intraocular retinoblastoma and the patient number included in most of them was also limited because of these factors. Most of them included from 7 to 11 eyes. In some of them, since only local toxicity was anticipated, there were no strict guidelines for dose escalation.

Our study found that 2 mg was well tolerated for periocular topotecan. This level was evaluated after nine courses in five eyes of four patients and was determined, not because we found DLT, but because we did not escalate beyond 2 mL, which was the limit in previous studies with carboplatin. Since our study included eyes that were facing imminent enucleation, it was not possible to assess its activity or its cumulative or long-term toxicity. Since we were not able to detect any significant toxicity with that dose level, we speculate that a higher dose may be administered using devices for ocular selective delivery such as sustained-release preparations. Because protracted topotecan regimens yielded better results, sustained release delivery systems are very appealing for this drug. Our group is developing a polymeric episcleral implant for the selective transscleral delivery of topotecan that was tested in animal models (Carabosso AM, et al. IOVS 2008;49: ARVO E-Abstract 3180).

Our previous animal data suggested that a significant amount of periocularly administered topotecan reaches the systemic circulation. However, the pharmacokinetic study showed that periocular topotecan resulted in lower than expected systemic lactone exposure, which was consistent with the low systemic toxicity we observed. In our cohort, AUC values were lower than 55 ng/mL·h which was substantially lower than our previous animal data, which showed a mean plasma AUC of lactone topotecan of 108.8 ng/mL·h after 1 mg of periocular topotecan. The estimation of vitreous levels for pharmacokinetic studies is not possible in humans with retinoblastoma, and so we speculate that a significant amount of topotecan might have reached the eye via a transscleral route without gaining access to the systemic circulation after periocular administration. Nevertheless, our results are limited to the small cohort studied, and they should be confirmed in a larger patient population. In addition, experience in children receiving intravenous topotecan with a pharmacokinetically guided protracted administration showed that a median dose of 2.7 mg/m² was necessary to reach the target AUC of 80 to 120 ng/mL·h of lactone topotecan. Our patients received up to 4 mg/m² of periocular topotecan and, even at the higher dosages, the plasma AUCs achieved in this study were in the range of 50 ng/mL·h. Thus, topotecan plasma levels observed after up to 4 mg/m² periocularly were significantly lower than the

### Table 3. Relationship between the Calculated Area under the Curve (AUC) and Dose

<table>
<thead>
<tr>
<th>Patient</th>
<th>Periocular Topotecan Dose (mg)</th>
<th>AUC (ng/mL·h)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>0.5</td>
<td>12.71</td>
</tr>
<tr>
<td>2</td>
<td>1.0</td>
<td>19.06</td>
</tr>
<tr>
<td>2</td>
<td>1.5</td>
<td>31.79</td>
</tr>
<tr>
<td>2</td>
<td>2.0</td>
<td>47.46</td>
</tr>
<tr>
<td>4</td>
<td>2.0</td>
<td>49.45</td>
</tr>
<tr>
<td>5</td>
<td>2.0</td>
<td>54.22</td>
</tr>
</tbody>
</table>

There was a linear relationship ($r^2 = 0.98$, $P = 0.003$).

No histopathologic evidence of drug toxicity was detected. No patient developed extraocular disease and all patients were alive at the time of this analysis. Additional information is shown in Table 1.

### Discussion

Our study found that periocular topotecan has a low local toxicity profile and its administration led to low plasma levels, resulting in no systemic toxicity in our cohort of heavily pretreated patients. Periocular chemotherapy has been recently investigated as a way to increase the ocular bioavailability of various drugs such as carboplatin and more recently etoposide and paclitaxel. To our knowledge, no other drug plasma AUC of lactone topotecan. Our previous animal data suggested that a significant amount of periocularly administered topotecan reaches the systemic circulation. Therefore, participants in this study were potentially at risk for this fatal complication, which could be avoided by timely enucleation. This possibility posed an ethical challenge for the design of the study, since a relatively large cohort would be needed for a precise estimation of MTD in case the study was done after traditional guidelines for dose escalation. Traditional phase I studies are usually designed to detect severe toxicity in a timely fashion, but the response rate is usually lower than 10% because of the inclusion of heavily pretreated patients. Therefore, we also anticipated a low response rate for our study. According to previous data on the use of periocular carboplatin and our animal study of periocular topotecan, we expected that severe toxicity from this treatment would occur infrequently. Therefore, we designed this study allowing for inpatient escalation if no moderate toxicity occurred. In case it occurred, even when it would not qualify for DLT, we would switch to a standard design with three patients per level and no inpatient escalation, to better estimate the MTD. Trial designs allowing for rapid inpatient escalation have been recently proposed to limit the exposure to subtherapeutic doses in the lower-dose cohorts for other malignancies, but we are not aware of a specific trial design that considers this particular situation in retinoblastoma. Moreover, there are few other phase I studies for intraocular retinoblastoma and the patient number included in most of them was also limited because of these factors. Most of them included from 7 to 11 eyes. In some of them, since only local toxicity was anticipated, there were no strict guidelines for dose escalation.

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![Figure 1](https://iovs.arvojournals.org/)
previously reported levels reached after intravenous administration, suggesting that a significant proportion of the drug was not released into the systemic circulation. In addition, a plasma pharmacokinetic profile was performed in one patient who received exactly the same dose, first perioricularly and then intravenously. In that case, the AUC of periorcular topotecan was half that obtained by the intravenous route, also suggesting transscleral diffusion to the eye. However, we measured only levels up to 4 hours of administration, and therefore we could not rule out slow clearance from the orbit.

In conclusion, this is the first report of the use of periorcular topotecan in children with retinoblastoma. This treatment modality is associated with mild local toxicity, and MTD was not reached, allowing for an escalation of topotecan to a dose of 2 mg. Its role as a single modality or in combination with other agents in the conservative treatment of retinoblastoma will be evaluated in further studies.

References