Intra-arterial Chemotherapy for the Management of Retinoblastoma

Four-Year Experience

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Objective: To determine whether intra-arterial chemotherapy is safe and effective in advanced intraocular retinoblastoma. Retinoblastoma often presents with advanced intraocular disease and, despite conventional treatment with intravenous chemotherapy and external beam radiation therapy, may still require enucleation.

Design: Single-arm, prospective registry from May 30, 2006, to May 30, 2010, at an ophthalmic oncology referral center with ambulatory care. A total of 95 eyes of 78 patients with unilateral or bilateral retinoblastoma were treated. The intervention was selective catheterization of the ophthalmic artery and injection of chemotherapy, usually melphalan with or without topotecan. Drug dosage was determined by age and angioanatomy. The main outcome measures were procedural success, event-free (enucleation or radiotherapy) ocular survival, and ocular and extraocular complications.

Results: Catheterization succeeded in 98.5% of procedures. There were 289 chemotherapy injections (median, 3 per eye). The Kaplan-Meier estimates of ocular event-free survival rates at 2 years were 70.0% (95% confidence interval, 57.9%-82.2%) for all eyes, 81.7% (95% confidence interval, 66.8%-96.6%) for eyes that received intra-arterial chemotherapy as primary treatment, and 58.4% (95% confidence interval, 39.5%-77.2%) for eyes that had previous treatment failure with intravenous chemotherapy and/or external beam radiation therapy. There were no permanent extraocular complications.

Conclusion: Our experience suggests that intra-arterial chemotherapy is safe and effective in the treatment of advanced intraocular retinoblastoma.


NUCLEATION REMAINS THE most common treatment for advanced intraocular retinoblastoma (Reese-Ellsworth [RE] group V), although some eyes can be salvaged with combinations of systemic chemotherapy, focal techniques, and external beam radiation (EBR) therapy.1-3 In 1955, Reese et al4 was the first to describe intra-arterial (IA) chemotherapy for retinoblastoma by “instillation under direct observation into the internal carotid artery on the side of the involved eye.” However, it was not until 1993 that Mohri5 reported using IA chemotherapy routinely with a technique of semi-selective IA infusion.5-7

Inspired by the Japanese experience, in May 2006, we started performing selective chemotherapy by direct intraophthalmic artery catheterization using modern microcatheters. In our early experience, we showed that IA chemotherapy could be successful in avoiding enucleation in advanced retinoblastoma, with acceptable ocular toxicity and minimal systemic toxicity,6-10 and that many treated eyes could retain or even improve retinal function.11 We subsequently expanded our indications for IA chemotherapy to allow its use as a primary treatment.12 Herein, we report our entire 4-year experience with IA chemotherapy for intraocular retinoblastoma.

METHODS

PATIENT POPULATION

From May 30, 2006, to May 30, 2010, we treated 78 patients with unilateral or bilateral intraocular retinoblastoma (95 eyes treated) with IA chemotherapy. Patients were enrolled in a phase 1/2 protocol until July 2009 and in a prospective registry thereafter. Our local institutional review board has approved these protocols, and informed consent was obtained from the parents. Results are reported as of May 30, 2010. For the phase 1/2 protocol, the inclusion criterion was having eyes that were candidates for enucleation; for the
prospective registry, the inclusion criterion was having eyes that were candidates for enucleation, intravenous chemotherapy, or EBR therapy. Exclusion criteria for both the phase 1/2 protocol and the prospective registry were as follows: having eyes that could be treated by local treatments (laser ablation, cryocoagulation, or radioactive plaque) without compromising vision; having eyes with very advanced disease (neovascular glaucoma or suspected invasion of postlaminar optic nerve, sclera, or anterior chamber); and extraocular invasion.

**PROTOCOL**

Every IA chemotherapy session was preceded by an ophthalmologic examination under anesthesia. These investigations included indirect ophthalmoscopy, fundus photography, ophthalmic ultrasonography, and electroretinography. In almost all cases, electroretinographic recordings were obtained at baseline and at all examinations under anesthesia. The amplitude of the response to a 30-Hz flicker was taken as our primary measure of retinal function, and reductions in amplitudes of at least 20% not associated with enlargement of retinal detachment (or associated with cataract) were taken as indicative of likely retinal toxicity. At the same examination under anesthesia, cryotherapy and/or laser ablation was performed as a curative treatment for small tumors, and for large tumors with the goal of increasing the permeability of the blood-retina barrier prior to IA chemotherapy if no retinal detachment was present. Intra-arterial chemotherapy sessions were repeated every 3 to 4 weeks. Decisions regarding the number of sessions were not standardized but depended on the findings of the examinations under anesthesia.

**IA CHEMOTHERAPY PROCEDURE**

The IA chemotherapy procedures were performed under general anesthesia with endotracheal intubation. We currently use a nasal decongestant (oxymetazoline hydrochloride, 0.05%) sprayed in the nostril on the treatment side to reduce the blush from the nasal mucosa. One femoral artery (alternatively right or left) was punctured, and a standard dose of heparin (70 IU/kg) was administered. In most cases, a straight microcatheter, such as the Marathon microcatheter (ev3, Irvine, California) or the Magic 1.5 microcatheter (Balt, Montmorency, France), was placed at the ostium of the ophthalmic artery (video, http://www.archophthalmol.com). Once the microcatheter was in place, selective angiography of the ophthalmic artery was performed to visualize the angioanatomy. Whenever the ophthalmic artery was not appropriate for selective catheterization (because it was too small or was making an acute angle off the internal carotid), 2 other techniques were used. The first alternative technique used the ipsilateral middle meningeal artery anastomosis to the orbit. We catheterized the middle meningeal artery and performed selective angiography to determine whether the orbital branch was well developed. If it was, then selective catheterization of this orbital branch permitted the injection of chemotherapy selectively into the orbital vasculature. If it was not well developed, then we either discontinued the procedure or elected to use the “Japanese technique,” which consists of placement of a temporary balloon to occlude the internal carotid artery above the origin of the ophthalmic artery and infusion into the internal carotid artery below the balloon.6

The chemotherapy drug(s) were diluted with saline to obtain a volume of 20 to 30 cm³ of solution that was injected manually by repeated small bolus (pulsatile injection) at a rate of 1 cm³/min. After drug delivery, the catheter was removed and hemostasis of the femoral artery was obtained with manual compression. After awakening, the child was kept in the postanesthesia recovery unit for 3 hours before being discharged home.

**RESULTS**

Intra-arterial chemotherapy was attempted in 95 eyes (17 of the 78 patients had both eyes treated at the same session). Table 1 summarizes patients’ demographic characteristics. According to the RE classification, 73 eyes were in the group Vb classification, 10 eyes were in group Va, 4 eyes were in group IV, and 8 eyes were in groups I-III. Previous treatments are summarized in Table 2. Fifty-two eyes (54.7%) were previously treated with intravenous chemotherapy or EBR therapy that was unsuccessful.

Two patients had their first IA chemotherapy session performed at our center, which was followed by additional IA chemotherapy sessions closer to home. The first treatment sessions are included in the toxicity assessment, but these eyes are not included in the eye-survival assessment (1 eye remains event-free, and the other was enucleated). Catheterizations were successful in 255 of 259 procedures (98.9%). The 235 successful procedures resulted in 221 unilateral and 34 bilateral IA catheterizations for a total of

| Table 1. Demographic Characteristics of 78 Patients Treated With IA Chemotherapy |
|--------------------------|-----|
| Characteristic           | No. |
| Sex                      |     |
| F                        | 43  |
| M                        | 35  |
| Age                      |     |
| Median (IQR), mo         | 18  |
| Minimum and maximum range| 1 mo-21 y |
| Disease                  |     |
| Unilateral               | 30  |
| Bilateral                | 48  |
| Previous contralateral enucleation | 15 |

Abbreviations: IA, intra-arterial; IQR, interquartile range.
of 289 IA injections of chemotherapy. The number of procedures ranged from 1 to 7 (mean, 3.2 per patient and 3.1 per eye; median and mode, 3 per patient and 3 per eye). Four procedures were unsuccessful: 3 unilateral and 1 bilateral failed attempt at catheterization. Catheterization failures occurred when we could not selectively catheterize the ophthalmic artery, when there was no access to the orbital vasculature through the middle meningeal artery, or when we did not want to use the Japanese catheterization technique because of a tortuous internal carotid artery or the very young age of the patient. Of these 5 eyes for which IA chemotherapy could not be completed, 1 was immediately enucleated, 3 were treated with intravenous chemotherapy, and 1 was treated with intravenous chemotherapy and EBR therapy. Of the 4 treated eyes, 2 came to enucleation, whereas the other 2 eyes remain under treatment.

**DRUG DOSAGE**

Melphalan was injected 275 times, in doses ranging from 2 to 7.5 mg (mean and mode, 4 mg). For melphalan, the dose was increased from 3.0 to 7.5 mg; at the latter dose, local toxicity was observed. We currently consider the standard dose of melphalan to be 5.0 mg for a 3-year-old child. Topotecan was used 97 times, always in association with melphalan or carboplatin, and the dose ranged from 0.15 to 1.5 mg (mean, 0.5 mg; mode, 0.3 mg). We started with a dose of 1.5 mg, but we noted significant decreases in the amplitudes of the ERGs at 4 weeks in the first set of patients. Therefore, we decreased the dose, and we currently use a standard dose of 0.4 mg for a 3-year-old child. Carboplatin was used 18 times, alone or in association with melphalan or topotecan, in doses ranging from 15 to 50 mg (mode, 30 mg). The dose was increased from 15 mg (minimally effective) to 50 mg (resulting in inflammatory reaction), and we currently use a standard dose of 30 mg for a 3-year-old child. Methotrexate was used twice (at 6 and 12 mg) but was found to be ineffective at these doses. **Table 3** reports the dosages that we used after the initial dose-finding phase.

**COMPLICATIONS**

**Procedural Complications**

There was no significant groin hematoma; 1 transient occlusion of the superficial femoral artery recanalized with aspirin after 1 week. There were 24 occurrences of significant bronchospasm during the procedure; in each instance, significant bronchospasm occurred during the second or later procedure, and when the microcatheter reached the cavernous carotid or ophthalmic arteries. Untreated bronchospasm could become severe, and then we would also observe bradycardia and hypotension. Thus, tidal volume and inspiratory pressure were carefully monitored: if bronchospasm appeared, catheterization maneuvers were discontinued and epinephrine bitartrate was injected intravenously. After cessation of bronchospasm, catheterization could be resumed. Six children developed an allergic reaction to iodinated contrast; this allergic reaction was prevented during subsequent procedures by the use of standard allergy premedication. There were no neurological complications.

**Ocular Complications**

Ten eyes developed a temporary inflammatory syndrome with periocular edema and redness. An avascular retinopathy with total visual loss was observed in 4 eyes. All 4 eyes belong to RE group V, and standard treatment in our institution would have been enucleation: 3 of them had already been unsuccessfully treated (1 with intravenous chemotherapy and EBR therapy, 1 with EBR therapy, and 1 with intravenous chemotherapy), and 1 had no prior treatment. All eyes were treated with multiple sessions of IA chemotherapy in excess of the doses we now use (Table 3). Three of the 4 eyes had additional treatments, which consisted of periocular injections of topotecan for 1 eye, radioactive plaque therapy, and cryotherapy. Of the 4 eyes with avascular retinopathy, 1 was preceded by a decrease in the amplitude of the ERG, 1 was preceded by an inflammatory reaction, 1 was preceded by both a decrease in the amplitude of the ERG and an inflammatory reaction, and 1 was not preceded by any clinical or ERG warning. Two of these eyes were enucleated; 2 are still in place but in phthisis. Three eyes developed a cataract; of these, 2 received recent radiation therapy. Transient red discoloration of the skin in the mesial frontal area (in the cutaneous territory of the ophthalmic artery) was seen in 14 cases after injection of melphalan.12 Twelve cases had temporary thinning or loss of eyelashes along the medial third of the upper eyelid.

**Chemotherapy Toxicity**

Significant neutropenia was observed following 29 of 255 IA treatment sessions (11.4%) in 18 patients, mostly when the total dose of melphalan exceeded 0.4 mg/kg of body weight. This toxicity was grade 3 (absolute neutrophil count, 1000-500/mm³) in 21 cases and grade 4 (absolute neutrophil count, <500/mm³) in 8 cases. One patient experienced fever and required admission for parenteral antibiotics. No child required transfusion of any blood products.

**CLINICAL RESULTS**

All children are alive. Two children developed metastatic disease, one 7 months after enucleation for painful phthisis and one 9 months after enucleation for re-

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**Table 2. Previous Treatments in 95 Eyes Treated With IA Chemotherapy**

<table>
<thead>
<tr>
<th>Previous Treatment</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>39 (41)</td>
</tr>
<tr>
<td>Intravenous chemotherapy</td>
<td>37 (39)</td>
</tr>
<tr>
<td>EBR therapy</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Intravenous chemotherapy and EBR therapy</td>
<td>14 (15)</td>
</tr>
<tr>
<td>Intravenous chemotherapy or EBR therapy</td>
<td>52 (55)</td>
</tr>
<tr>
<td>Radioactive plaque</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Periocular chemotherapy</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Laser ablation or cryotherapy</td>
<td>36 (38)</td>
</tr>
</tbody>
</table>

Abbreviations: EBR, external beam radiation; IA, intra-arterial.

*aThe total is greater than 100%.
current disease. Both were treated with aggressive intravenous chemotherapy and local radiotherapy and are currently doing well. No child developed a trilateral retinoblastoma. The Kaplan-Meier curves of eye survival until enucleation or EBR therapy are presented in Figure 1 for all RE groups and in Figure 2 for RE group V. The Kaplan-Meier estimates of ocular event-free survival at 2 years were 70.0% (95% confidence interval [CI], 57.9%-82.2%) for all eyes, 81.7% (95% CI, 66.8%-96.6%) for eyes that received IA chemotherapy as primary treatment, and 58.4% (95% CI, 39.3%-77.2%) for eyes that were previously treated with intravenous chemotherapy and/or EBR therapy. For RE group V eyes, the Kaplan-Meier estimates of ocular event-free survival at 2 years were 66.5% (95% CI, 53.4%-79.6%) for all group V eyes, 80.5% (95% CI, 65.0%-96.1%) for group V eyes that received IA chemotherapy as primary treatment, and 51.5% (95% CI, 30.5%-72.5%) for group V eyes that were previously treated with intravenous chemotherapy and/or EBR therapy. With a follow-up of 1 to 29 months (median, 13 months), none of the 12 eyes in RE groups I-IV had to be enucleated or irradiated. Enucleation was performed in 19 of the 83 group V eyes because of tumor growth or insufficient tumor regression (mostly vitreous seeds) despite IA chemotherapy. One of these eyes was at first treated by EBR therapy but finally had to be enucleated. The additional treatments performed during or after IA chemotherapy are detailed in Table 4. Figure 3 shows an example of advanced intraocular retinoblastoma treated with IA chemotherapy.

**COMMENT**

It has been a therapeutic challenge to avoid enucleation and to preserve vision in eyes with advanced retinoblastoma. Focal treatments such as laser ablation or cryotherapy are effective only on small tumors without extensive vitreous seeds; advanced tumors require tumor reduction with intravenous chemotherapy, radiation, or both, to avoid enucleation. EBR therapy is the oldest form of ocular salvage therapy for large retinoblastoma. It is able to save up to 53% of eyes with the most advanced (RE group Vb) disease, but it has frequent (52%) adverse effects such as cataracts, radiation retinopathy, and vitreous hemorrhage. Furthermore, radiotherapy increases the incidence of nonocular secondary cancers. Since the 1990s, EBR therapy has been replaced by intravenous chemotherapy as first-line treatment for retinoblastoma, although it is still used as second-line treatment after the failure of intravenous chemotherapy. Intravenous chemotherapy (chemoreduction) is most commonly performed with 2 or 3 agents (carboplatin and vincristine sulfate with melphalan) would exceed 0.5 mg/kg.
or without etoposide phosphate) given monthly for 6 to 9 months and is associated with monthly focal ophthalmologic treatments.

For low-grade retinoblastoma, chemoreduction with focal treatments is generally effective: 100% effective for tumors in the RE groups I-IV for Murphree et al, 100% and 66% event-free (EBR therapy or enucleation) eye survival for tumors in the RE groups I-III and RE group IV, respectively, for Friedman et al., and 71% effective for tumors in the RE groups I-III for Beck et al. In Shields et al, EBR therapy was necessary in 10% of eyes with retinoblastoma in the RE groups I-IV and enucleation was necessary in 15% of eyes with retinoblastoma in the RE groups I-IV, with 38% of eyes with unilateral retinoblastoma requiring either treatment. Using conservative ocular therapy and chemomotherapy, Lumbroso-Le Rouic et al found that enucleation and EBR therapy were not necessary for eyes in the RE groups I-II and that enucleation or EBR therapy was necessary in 11% of eyes in the RE groups III-IV. Our results are comparable with the best results in the literature, because none of the 12 eyes in the RE groups I-IV in our series had to be enucleated or irradiated.

In contrast to the good outcomes with intravenous chemotherapy and focal therapy observed in the eyes with retinoblastoma in the RE groups I-IV, in the eyes with retinoblastoma in the RE group V, these modalities are often insufficient. Using intravenous chemotherapy and focal treatments, Friedman et al and Cohen et al found that the event-free (EBR therapy or enucleation) eye survival rate was 47% and 34%, respectively. For Shields et al, EBR therapy was necessary in 47% of eyes and enucleation was necessary in 53% of eyes, with 100% of eyes with unilateral retinoblastoma requiring either treatment. For Lumbroso-Le Rouic et al, EBR therapy was necessary in 29% of eyes and enucleation was necessary in 53% of eyes. As such, IA chemotherapy appears more likely to be curative. In our series, the event-free eye survival rate following IA chemotherapy was 80.5% for eyes in the RE group V that received IA chemotherapy as primary treatment; for eyes that had previous treatment with intravenous chemotherapy and/or EBR therapy, the event-free survival rate was still 51.5%.

Intravenous chemotherapy has many adverse effects that we did not observe in this series: nausea and vomiting, hair loss, and myelosuppression commonly occur with intravenous chemotherapy. Myelosuppression may be severe, resulting in systemic infections requiring antibiotics, transfusion of platelets or red blood cells, and nonspecific gastrointestinal toxicity with dehydration and failure to thrive. Long-term risks are not negligible, such as ototoxicity after a high dose of carboplatin and acute myelogenous leukemia after etoposide. In contrast, we have seen minimal toxicity with IA chemotherapy because small doses of chemotherapy were used. Only 1 child had a fever associated with a low absolute neutrophil count and was admitted for a 3-day course of intravenous antibiotics.

In our study, we chose melphalan as our main chemotherapy agent based on a large Japanese study, which itself was based on the high activity of melphalan in cultured human retinoblastoma cells. Melphalan has a short half-life (1.5 h), which makes it ideally suited for exploiting the first-pass benefit of IA chemotherapy. The intravenous usage of melphalan is limited by severe myelosuppression, but it has been well tolerated in our study when given intra-arterially at doses of less than 0.5 mg/kg. Topotecan was added to melphalan later in our study, for treating the most difficult tumors with extensive vitreous seeds, based on its activity when associated with alkylating agents in rodent models of retinoblastoma and on our prior experience with periocular injection. Another advantage of melphalan and topotecan is that they are not used in protocols of intravenous chemotherapy for retinoblastoma, so the tumor may not have developed specific resistance when patients are referred after failure of intravenous chemotherapy. Carboplatin was used intra-arterially if initial treatment with melphalan and topotecan was not successful, or in case of simultaneous bilateral injections when infusion of melphalan in both eyes would expose the patient to a dose of melphalan greater than 0.5 mg/kg. A weakness of our study is that we did not follow a strict protocol: there was much variation in the types of drugs used, in the time intervals between IA chemotherapy procedures, and in the use of adjuvant therapy. Also, we cannot compare the effectiveness of single-drug (mostly melphalan) vs multiple-drug (mostly melphalan and topotecan) injections, because we used multiple drugs in the most advanced tumors from the first IA chemotherapy or if the findings of examinations under anesthesia were not satisfactory after 1 or 2 IA chemotherapy treatments.

Our experience differs from the Japanese experience in the indications for treatment, the method of catheter-
ization, and the drug dosage. We prefer to use modern microcatheters to selectively catheterize the ophthalmic artery, rather than a balloon catheter that temporarily occludes the internal carotid artery. Instead of using body weight or body surface area, we used a drug dosage that was based on the arterial territory to be infused. We have shown previously in various protocols of IA chemotherapy for brain tumors that neurological toxicity was related to the dosage per arterial territory infused and not to dosage per body weight or body surface area.32 We use the same concept for ophthalmic artery IA chemotherapy, and we base the drug dosage on age (used as an approximation for eye size) and angioanatomy. This concept has been successful for minimizing retinal toxicity. With the doses we currently recommend (Table 3), we have not had any permanent ocular toxicity: all toxicity occurred at higher doses, given when the tumors were not controlled using standard doses. However, we routinely use an ERG to evaluate the potential toxic effect of each dose and adjust the next dose as indicated.

In conclusion, it appears from our experience that IA chemotherapy is safe and effective in the treatment of advanced intraocular retinoblastoma. Intra-arterial chemotherapy has transformed the treatment of intraocular retinoblastoma in our center: it has replaced intravenous chemotherapy and we base the drug dosage on age (used as an approximation for eye size) and angioanatomy. This concept has been successful for minimizing retinal toxicity. With the doses we currently recommend (Table 3), we have not had any permanent ocular toxicity: all toxicity occurred at higher doses, given when the tumors were not controlled using standard doses. However, we routinely use an ERG to evaluate the potential toxic effect of each dose and adjust the next dose as indicated.

Submitted for Publication: May 20, 2010; final revision received November 29, 2010; accepted November 30, 2010.

Published Online: February 14, 2011. doi:10.1001/archophthalmol.2011.5

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Author Contributions: All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Financial Disclosure: None reported.


Additional Contributions: We thank Nicole J. Savage, MS, for statistical analysis.

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