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;8-10 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 focal treatments (laser ablation, cryocoagulation, or radioactive plaque) without compromising vision; having eyes with very advanced disease (necovascular 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 examinations 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 flush 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 Marathom 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.

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.

| Table 1. Demographic Characteristics of 78 Patients Treated With IA Chemotherapy |
|-----------------|-------|
| Characteristic  | No.   |
| Sex             |       |
| F               | 43    |
| M               | 35    |
| Age             |       |
| Median (IQR), mo| 18 (9-32) |
| Minimum and maximum range | 1 mo-21 y |
| Disease         |       |
| Unilateral      | 30    |
| Bilateral       | 48    |
| Previous contralateral enucleation | 15 |

Abbreviations: IA, intra-arterial; IQR, interquartile range.

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 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 intraventricular chemotherapy and EBR therapy. Of the 4 treated eyes, 2 came to enucleation, whereas the other 2 eyes remain under treatment.

**DRUG DOSAGE**

Methotrexate was used twice (at 6 and 12 mg) but was found to be ineffective at these doses. Melphalan was used twice (at 6 and 12 mg) but was found to be ineffective at these doses. 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 therapy</td>
<td>37 (39)</td>
</tr>
<tr>
<td>EBR therapy</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Intravenous therapy 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 therapy</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.

*The 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, 39.5%-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.

**Table 3. Current Drug Dosages According to Age**

<table>
<thead>
<tr>
<th>Drug</th>
<th>3-6 mo</th>
<th>6-12 mo</th>
<th>1-3 y</th>
<th>≥3 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melphalan</td>
<td>2.5</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Topotecan</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
<td>0.4</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>Not tested</td>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
</tbody>
</table>

*Dose is increased if the ophthalmic artery has large extraocular branches or if there is insufficient tumor reduction from the previous cycle. Dose is decreased if there was previous treatment with intravenous chemotherapy and radiation (especially if recent), if the microcatheter is in “wedge flow” in the ophthalmic artery, if there is an inflammatory reaction after the previous cycle, if there is a decreased amplitude on electrotoretinogram after the previous cycle, if parents noted vision decrease (not reliable in young children), and/or if bilateral treatment is planned and the total (body) dose of melphalan would exceed 0.5 mg/kg.

**Table 4. Additional Treatments During or After IA Chemotherapy in 95 Eyes**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>22 (23)</td>
</tr>
<tr>
<td>Local cryotherapy or laser ablation</td>
<td>54 (57)</td>
</tr>
<tr>
<td>Radioactive plaque</td>
<td>9 (9)</td>
</tr>
<tr>
<td>Intravenous chemotherapy</td>
<td>3 (3)</td>
</tr>
<tr>
<td>EBR therapy</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Pericocular chemotherapy</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Pericocular steroid injection</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Retinal surgery</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Required enucleation</td>
<td>19 (20)</td>
</tr>
</tbody>
</table>

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

*The total is greater than 100%.

**Table 4. Additional Treatments During or After IA Chemotherapy in 95 Eyes**

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.14 Furthermore, radiotherapy increases the incidence of nonocular secondary cancers.15-18 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...
venous chemotherapy. Myelosuppression may be severe, loss, and myelosuppression commonly occur with intra-
we did not observe in this series: nausea and vomiting, hair
free survival rate was still 51.5%.
mary treatment; for eyes that had previous treatment with
in the RE group V that received IA chemotherapy as pri-
resulting in systemic infections requiring antibiotics, trans-
fusion of platelets or red blood cells, and nonspecific gas-
trointestinal toxicity with dehydration and failure to thrive.27
Long-term risks are not negligible, such as ototoxicity af-
to a high dose of carboplatin26 and acute myelogenous leu-
kemia after etoposide.28 In contrast, we have seen minimal
toxicity with IA chemotherapy because small doses of che-
motherapy 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 che-
motherapy agent based on a large Japanese study, which
itself was based on the high activity of melphalan in cul-
tured human retinoblastoma cells.6 Melphalan has a short
half-life (1.5 h), which makes it ideally suited for ex-
ploting the first-pass benefit of IA chemotherapy. The
intravenous usage of melphalan is limited by severe my-
elsuppression, 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 vit-
reous seeds, based on its activity when associated with
alkylating agents in rodent models of retinoblastoma30
and on our prior experience with periocular injection.31
Another advantage of melphalan and topotecan is that
they are not used in protocols of intravenous che-
therapy 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 mel-
phalan and topotecan was not successful, or in case of
simultaneous bilateral injections when infusion of mel-
phalan in both eyes would exposing the patient to a dose of melphalan greater than 0.5mg/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 mul-
tiple-drug (mostly melphalan and topotecan) injec-
tions, because we used multiple drugs in the most ad-
vanced tumors from the first IA chemotherapy or if the
tions, because we used multiple drugs in the most ad-
anced tumors from the first IA chemotherapy or if the
way to observe in this series: nausea and vomiting, hair
loss, and myelosuppression commonly occur with intra-
venous chemotherapy.26 Myelosuppression may be severe,
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.\textsuperscript{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 EBR therapy when the tumor is too large to be controlled with focal ophthalmological therapies.

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REFERENCES