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Rev Inves Clin. 2016;68:137-42 ORIGINAL ARTICLE

Globe Salvage With Intra-Arterial Topotecan-Melphalan Chemotherapy in Children With a Single Eye

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ABSTRACT

Introduction: Intra-arterial chemotherapy is a novel therapeutic modality for retinoblastoma patients. Intra-arterial chemotherapy involves the administration of a super-selective drug through the ophthalmic artery, resulting in better ocular penetration and low systemic toxicity. **Objective:** The aim of this report was to evaluate the feasibility of intra-arterial chemotherapy in a large referral center in Mexico City. **Methods:** We included patients with bilateral retinoblastoma, one enucleation, and active disease in the other eye after at least two courses of systemic chemotherapy combined with topical treatments. All patients were treated with three courses of a combination of melphalan 4 mg and topotecan 1 mg. Patients were examined under general anesthesia three weeks after each chemotherapy cycle. **Results:** From 14 eligible patients, three could not be treated due to inaccessibility of the ophthalmic artery. A complete response was observed in 5/11 patients, three in Stage C according to the International Classification for Intraocular Retinoblastoma, one in Stage D, and one in Stage B. The eyes of three patients were enucleated as a result of active/progressive disease, one in Stage B and two in Stage D. Eye preservation was 55% after a mean follow-up of 171 days (range 21-336). **Conclusions:** Super-selective intra-arterial chemotherapy is safe and effective for preventing the enucleation of 55% of affected eyes in this group of patients. (REV INVES CLIN. 2016;68:137-42)

Key words: Retinoblastoma. Intra-arterial chemotherapy. Ocular rescue. Melphalan. Topotecan.

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INTRODUCTION

Retinoblastoma is the most frequent ocular malignancy in children[1]. In Mexican infants and toddlers it is the second most frequent solid neoplasia after brain tumors[2]. In developed countries, including the USA, retinoblastoma is a curable disease, with ocular survival being a priority[3].

Systemic chemotherapy, either in a neoadjuvant or adjuvant setting after enucleation, is currently the standard treatment. However, since the ocular volume represents less than 1% of the body surface and there is low drug penetration into the vitreous chamber, the actual amount of the chemotherapy agent reaching the eye remains quite low when delivered intravenously and is also systemically toxic[4].

Intra-arterial chemotherapy (IAC) involves super-selective drug administration through the ophthalmic artery, resulting in better penetration of the ocular structures and lower systemic toxicity[5]. After various treatment failures it was first used as rescue therapy in recurrent retinoblastoma, but also proved to be effective as first-line treatment in Group C and D eyes, according to the International Classification of Intraocular Retinoblastoma (ICIRB)[6]. Furthermore, the salvage of Group E eyes has been reported[7]. The ICIRB is the newest staging system. It classifies intraocular retinoblastoma into five groups from A to E, based on the size and location of the tumor, and predicts the possibilities of rescuing the eye(s) (Table 1).

Although IAC has been known since 2004, only recently has it been applied in Mexico. Therefore, the aim of this study was to evaluate the feasibility of IAC in a referral center of a country with a middle-income population.

Table 1. International Classification for Intraocular Retinoblastoma (ICIRB)

Group	Description
A Eyes with small discrete tumors away from critical structures.	Tumors ≤ 3 mm confined to the retina. > 3 mm from the foveola and > 1.5 mm from the optic nerve. Non-vitreous or subretinal seeding.
B Eyes with no vitreous or subretinal seeding and discrete retinal tumor of any size or location.	Tumors > 3 mm, no vitreous or subretinal seeding. Subretinal fluid > 5 mm from the base of the tumor.
C Eyes with only focal vitreous or subretinal seeding and discrete retinal tumors of any size and location.	Seeding local, fine, and limited. Tumors discrete and of any size and location, up to one quadrant of subretinal fluid.
D Eyes with diffuse vitreous or subretinal seeding and/or massive, non-discrete endophytic or exophytic disease. Eyes with more extensive seeding than Group C.	Massive and/or diffuse intraocular disseminated disease. More than one quadrant of retinal detachment. Fine greasy vitreous seeding or avascular masses. Subretinal seeding, plaque-like.
E Eyes that have been destroyed anatomically or functionally by the tumor. Eyes with one or more than the following:	Irreversible neovascular glaucoma. Massive intraocular hemorrhage. Aseptic orbital cellulitis. Tumor anterior to anterior vitreous face. Tumor touching the lens. Diffuse infiltrating; retinoblastoma. Phthisis or pre-phthisis.

MATERIALS AND METHODS

Study design and patients

This was a prospective, longitudinal study. Patient inclusion criteria were: age > 12 months, previously diagnosed bilateral disease, enucleation of one eye, confirmation of active disease in the remaining eye, and having received at least two courses of systemic chemotherapy combined with local treatments (photocoagulation, thermotherapy) six weeks prior to intra-arterial treatment (Table 2). All patients had a complete physical examination to demonstrate active disease; the fundi were examined under anesthesia and RetCam images were obtained. Three patients with extraocular disease, glaucoma, or prior external-beam radiotherapy within six weeks of the study treatment were excluded. The study was conducted following the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the National Pediatrics Institute (Instituto Nacional de Pediatría, INP). Legal representatives of all enrolled patients provided written informed consent for the procedures.

Table 2. Results according to disease group

Patient no.	Previous treatment	ICIRB classification	Status after 3 IAC treatments	Follow-up (days)
1	Systemic chemotherapy + photocoagulation	C	Partial response	133
2	Systemic chemotherapy + photocoagulation	C	No response	91
3	Systemic chemotherapy + photocoagulation	D	Partial response	21
4	Systemic chemotherapy + photocoagulation	B	No response	149
5	Systemic chemotherapy + photocoagulation	D	Complete response	336
6	Systemic chemotherapy + photocoagulation	C	Complete response	289
7	Systemic chemotherapy + photocoagulation	D	No response	330
8	Systemic chemotherapy + photocoagulation	C	Complete response	122
9	Systemic chemotherapy + photocoagulation	C	Complete response	86
10	Systemic chemotherapy + photocoagulation	D	Partial response	282
11	Systemic chemotherapy + photocoagulation	B	Complete response	121

IAC: intra-arterial chemotherapy; ICIRB: International Classification for Intraocular Retinoblastoma.

Intra-arterial chemotherapy

All patients were treated by the same interventional neuroradiologist, following the technique described by Abramson, et al.[4] (Fig. 1). Drugs used were melphalan at a dose of 4 mg diluted in 20 ml of 0.9% sodium chloride, and topotecan at a dose of 1 mg diluted in 20 ml of 0.9% sodium chloride, each administered over 30 minutes for a total of one hour; drug dosages were based on the patient's age as per Gobin, et al.[8]. After treatment an angiography was obtained to detect any complications from the treatment.

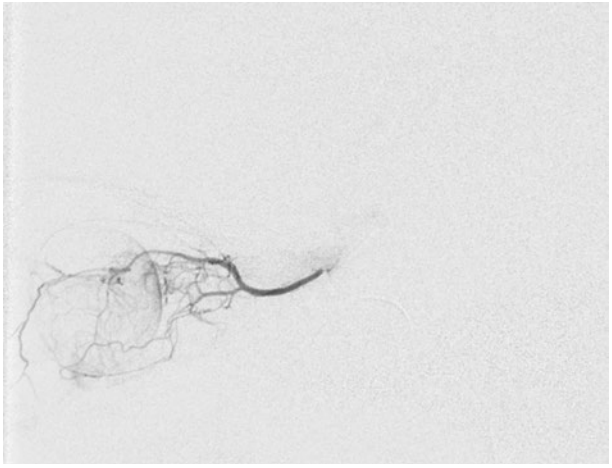
Patients were evaluated under general anesthesia with RetCam images 21 days after each IAC. Treatment consisted of three courses administered at 28-day intervals. Response was defined by our workgroup as follows: no response, if tumor size reduction was < 25% from the original size; partial response, if reduction was 25-50%; good response, if reduction was 50-75%; and complete response, if the reduction was > 75%.

All adverse events relating to the treatment procedure were recorded. The final response was evaluated by RetCam imaging after the third IAC cycle.

Statistical analysis

Analysis was based on the ICIRB stage at the time of diagnosis compared with the last RetCam image. Statistical analysis was performed using the SPSS program (IBM SPSS Statistics v.19, Chicago, IL.). Kaplan-Meier curves were constructed for globe rescue analysis.

Figure 1. Digital subtraction of ophthalmic artery after contrast infusion.



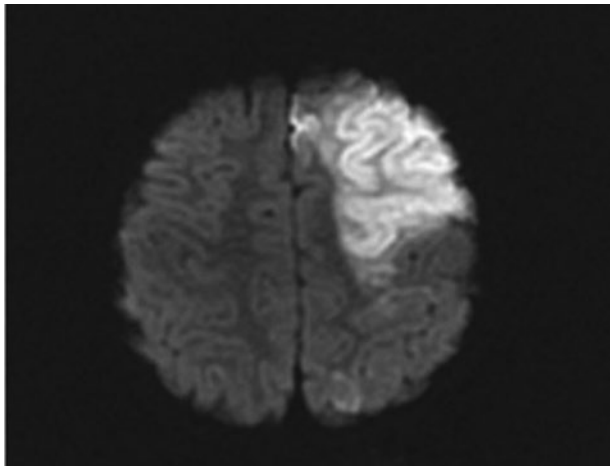
RESULTS

From 14 patients eligible for the study, three could not be treated due to inaccessibility of the ophthalmic artery. In the 11 treated patients, evaluation was performed after three IAC courses.

The mean age at presentation was 22.6 months (range, 12-36); seven patients were male and four were female. The group distribution included: two eyes in Group B, five eyes in Group C, and four eyes in Group D. Results of IAC according to the initial disease stage are shown in table 2.

A complete response was observed in 5/11 patients, one patient in Group B, three in Group C, and one in

Figure 2. Magnetic resonance imaging showing cerebral ischemia in patient no. 8 after the first course of intra-arterial chemotherapy.



Group D. In three patients, a partial response was observed, including one patient in Group C (patient no. 1), and two in Group D (patients nos. 3 and 10). These patients received further treatment (intravenous topotecan) to avoid enucleation. In one of the two Group D patients, disease progressed and the eye had to be enucleated. Of the three remaining patients, one had a stable disease (patient no. 2, Group C), but developed vitreous seeds and was rescued with intravitreal melphalan. The other two patients, one in Group B (patient no. 4) and one in Group D (patient no. 7), had progressive disease and the eyes had to be enucleated.

During the first treatment course, two of 11 patients developed acute complications. Patient no. 7 had nausea, vomiting, and a prolonged 48-hour hospitalization, but recovered completely. Patient no. 8 developed hemiparesis and severe ipsilateral headache, evaluated by neurological examination and magnetic resonance imaging. The latter revealed an ischemic area in the left parietal lobe, ipsilateral to the treated eye (Fig. 2). The angiography performed before melphalan administration showed no anatomical abnormalities, but the access to the ophthalmic artery was prolonged (30 minutes); perhaps this technical complication led to vasospasm and ischemia. The patient recovered completely one month later, after which she received the other two courses. No hematological toxicity or other systemic or local complications were observed.

Figure 3. Event-free (no enucleation) survival of the whole group.

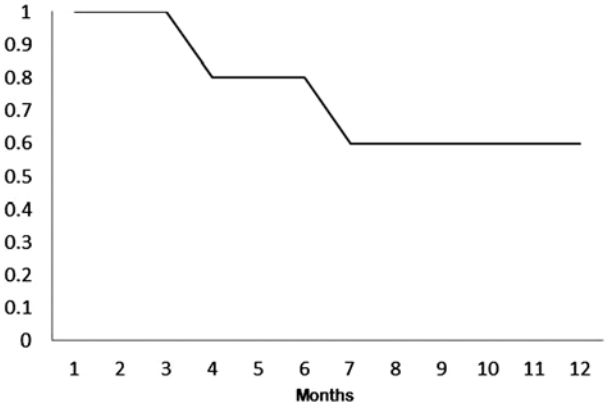
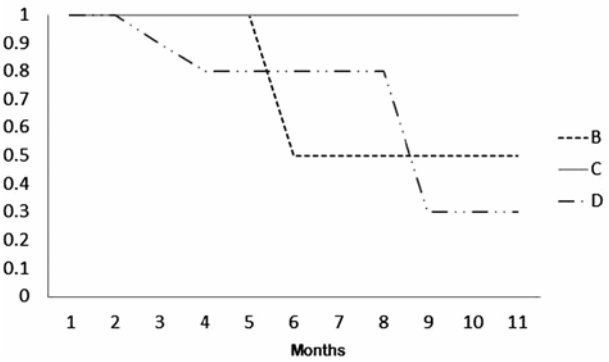


Figure 4. Event-free survival according to the initial ocular stage.



Kaplan-Meier curves showed eye preservation in 55% of cases (n = 6) after a mean follow-up of 171 days (range, 21-336) (Fig. 3). All Group C patients were rescued, as were 50% in Group B and 30% in Group D. The majority of eyes had Group C disease, and only two eyes belonged to Group B; establishing firm conclusions in the latter group was impossible since one of the two Group B eyes progressed and had to be enucleated (Fig. 4).

DISCUSSION

Intra-arterial chemotherapy was first described in the 1960s by Ellsworth[9], then further developed in Japan and reported by Kaneko, et al. in 2003[10]. In 2006, Abramson, et al.[4] modified the technique described by Kaneko, et al. by selectively introducing a microcatheter into the ophthalmic artery to directly administer

melphalan, carboplatin, and topotecan. Results of this therapy were reported in 2010, with 28 eyes initially treated in 23 patients over a three-year period. Only one eye had to be enucleated (3.5%) due to disease progression, and no eyes were enucleated as a result of treatment-related adverse events. Overall ocular survival was 100% at one year and 89% after two years of follow-up[3].

Recently, Absamson, et al. reported their results with IAC from 2006 to 2015; their enucleation rates decreased from over 95% to less than 10% in advanced-stage disease[11].

In middle-income countries such as Argentina, IAC is used as rescue therapy after retinoblastoma relapse and is more effective than periocular and intravenous chemotherapy[12], preserving up to 50% of eyes. Our study has shown that according to published guidelines, IAC can be safely administered in our local setting to patients with resistant or progressive retinoblastoma. Efficacy was satisfactory, with a complete response in 5/11 patients with bilateral disease and a single eye that did not respond to previous treatment with photocoagulation and systemic chemotherapy. Furthermore, 55% of eyes were rescued, thus avoiding enucleation. These results are comparable to those in centers with greater experience and similar patient cohorts, as reported by Gobin, et al.[8]. However, further patient accrual and longer follow-up periods are required to evaluate long-term eye preservation and drug toxicity. One of the major prognostic factors for retinoblastoma is its stage at the time of diagnosis. When IAC is used as the primary treatment modality, 80% of eyes can be saved, mostly in Groups C and D. Although advanced disease (E stage) is rare in developed countries, 50% of cases can also be rescued with IAC[13].

Experienced medical centers (i.e. treating more than 50 eyes each year) have adopted this treatment modality as their primary approach in Groups B, C, and D eyes and as rescue therapy at any stage[14]. In Mexico, the usual advanced stage at diagnosis[15] does not allow this type of treatment as the primary approach, although at our referral institution, an increasing number of patients are being diagnosed in earlier disease groups.

Although there is no established standard in terms of the types of drugs to be used for intra-arterial treatment, animal studies have shown that melphalan and topotecan can achieve therapeutic concentrations in the eye without significant levels in plasma[16,17]. Abramson, et al. have reported the combined use of melphalan (3.0-7.5 mg), topotecan (0.3-0.5 mg), and carboplatin (15-30 mg)[5], whereas Gombos, et al. used exclusively melphalan at a dose of 3-5 mg, increasing it up to 7.5 mg according to tumor response[18]. In addition, Munier, et al.[19] consolidated intra-arterial treatment with local therapies. In patients with a low response to melphalan only, Shields, et al. added 30 mg of carboplatin to 3 mg of melphalan[7] and demonstrated that the simultaneous use of two or more drugs is more effective than a single drug[20]. In our study, a combination of melphalan and topotecan was used. In all cases, we used 4 mg of melphalan and 1 mg of topotecan according to the patient's age[8].

Intra-arterial chemotherapy is a complex procedure that is not exempt from complications. In our series, we report one neurological event with no long-term sequelae. The patient presented this event after the first IAC, but we still completed three IAC sessions, obtaining a full response and rescuing the affected eye. The ocular and extraocular complications of the procedure have been reported by Monroy, et al.[21]. In our center we have not experienced any other complications.

Intra-arterial treatment is not a completely new treatment modality, but has existed for more than 20 years as first- or second-line treatment in certain parts of the world[18]. In the last eight years this treatment modality has been reconsidered, has been modified, and has been increasingly used as a conservative treatment modality, with possibly lesser toxicity when managing retinoblastoma. A recent survey by Grigorovski, et al.[14] reported that 63 centers in 35 countries were familiar with the procedure as an ocular rescue treatment. In Mexico, a country with 10-11 million children under the age of five years[22], this type of therapeutic procedure had never been used, and only four medical centers nationwide have the capacity to perform it.

After comparing the costs of this procedure with the number and duration of hospitalizations and the complications resulting from the usual treatment modalities, IAC is clearly cost-effective.

In conclusion, retinoblastoma is a highly curable cancer when diagnosed early and treated effectively. Thus, rescue of these eyes should become a priority in developing countries. Intra-arterial chemotherapy is an effective and safe therapeutic modality, which fosters the rescue of eyes with intraocular retinoblastoma and precludes the need for external-beam radiotherapy. Over half of pretreated eyes were salvaged, so it should be considered as the first option when rescuing single eyes in patients with retinoblastoma[23]. Although IAC could be more efficient if used as the primary treatment, this possibility needs to be further proven at our institution. This treatment modality requires expensive material resources and the highly specialized expertise of a multidisciplinary team, and should therefore be concentrated in a few centers in developing countries. In the long-term it could result in better cost-effectiveness, thus avoiding the additional costs of hospitalization and development of systemic complications.

Education is pivotal, particularly among healthcare professionals, since early detection of retinoblastoma leads to a higher proportion of intraocular local treatments for disease eradication.

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