

# Efficacy of second-course intra-arterial chemotherapy in children for advanced retinoblastoma recurrence after intra-arterial chemotherapy

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## ABSTRACT

**Purpose:** The present study determined the efficacy and toxicity of second-course intra-arterial chemotherapy (IAC) in advanced retinoblastoma (RB) recurrence in children following failed initial IAC.

**Materials and Methods:** A total of 24 child patients with unilateral or bilateral intra-ocular advanced RB (IIRC Group D and Group E) undergoing second-course IAC treatment after initial intra-arterial chemotherapy between September 2011 and November 2016 were enrolled. Global salvage, ocular adverse events, and systemic adverse events were assessed.

**Results:** Following second-course IAC, 15 (62.5%) showed complete control at 34 months follow-up, while 8 cases (33.3%) failed the treatment and 1 patient with metastatic disease (4.2%) eventually died of brain metastasis after refusing treatment. Ocular adverse events included eyelid edema (n=12), ptosis (n=5), forehead erythema (n=5), enophthalmos (n=3), and cataract (n=2). None of the patients had systemic adverse events, such as stroke or sepsis. Also, no secondary neoplasms and technical complications were observed.

**Conclusion:** Second-course IAC is a potential alternative to enucleation in children with advanced RB, who fail an initial course of IAC. However, patients with advanced RB should be managed at experienced centers in order to consider all the alternatives before enucleation.

**Keywords:** retinoblastoma; second-course intra-artery chemotherapy; intravenous chemotherapy

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## INTRODUCTION

Retinoblastoma (RB) is a common cancer in children that is diagnosed in approximately 8,000 new cases each year worldwide. It can affect one or both eyes (unilateral or bilateral RB); bilateral RB is always inherited (1). Nonetheless, RB is one of the most successfully treated pediatric malignant tumors with treatment involving global conservation utilizing intravenous chemotherapy (IVC) or intra-arterial chemotherapy (IAC) coupled with focal therapy (laser therapy or cryotherapy) and enucleation of the eye

(2-5). IAC, as one of the primary treatments currently available, has been employed as a primary or secondary therapy, following the failure of other treatments including IVC in order to avoid significant complications by IVC (2, 3).

However, the recurrence rate of RB was reported to be 19% (6), and advanced RB recurrence rate was up to 29% (7) after IAC. For eyes with RB that fail initial IAC, enucleation is often the main alternative. However, if the other eye has been enucleated, other options are sought to attempt to save the remaining eye and minimize the impact on life. Thus, is IAC an option for eyes with recurrent disease following the initially successful IAC treatment? In a retrospective study including 12 patients, enucleation was considered as the only remaining option; however, eye removal was avoided in 8 (67%) by second-course IAC in patients not only with advanced tumors but also early stage patients (8). Nevertheless, only limited information is available regarding the efficacy and toxicity of IAC treatment as second-course for advanced RB recurrence after initial intra-arterial chemotherapy. Therefore, in this study, we reviewed our experience with second-course IAC using a combination of treatment agents in children with advanced RB, who failed initial IAC.

## MATERIALS AND METHODS

## Patients

The present retrospective study was approved by the Ethics committee of Guangzhou Women and Children's Medical Center. The study participants were patients <16-year-old with unilateral or bilateral intraocular advanced RB (IIRC Group D and Group E) undergoing second-course IAC treatment after initial intra-arterial chemotherapy between September 2011 and November 2016. Patients > 16 years of age or if the RB was classified as IIRC Group A, Group B, and Group C or at an advanced stage, eyes with visible tumor extension into the optic nerve, uvea, anterior segment, or sclera were excluded. Written informed consent was obtained from the caregivers or guardians on behalf of the children enrolled in this study.

## Methods

### Technique and treatment

Our technique of IAC has been described elsewhere (9, 10). All IAC procedures were performed by interventional radiologists under general anesthesia. The femoral artery was punctured with a 4-French (4-F) arterial sheath using Seldinger technique, followed by administration of heparin (75 IU/kg). Under X-ray guidance, the ipsilateral internal carotid artery was catheterized with a 4-F Cobra guide catheter (Terumo, Tokyo, Japan). Serial arteriograms were utilized to visualize the ocular and cerebral vasculature and determine the path of the ophthalmic artery from the internal carotid artery. Using fluoroscopy and road mapping, the ophthalmic artery was catheterized using a 1.7-F microcatheter (v3 Neurovascular Inc., Irvine, CA, USA). When the microcatheter was placed at the ostium of the ophthalmic artery, an angiogram of the ophthalmic artery was taken. After the infusion of agents was concluded, the microcatheter was withdrawn and the sheath removed. Subsequently, the hemostasis of the femoral artery was achieved by manual compression for 10–15 min. Patients were monitored overnight before discharge. Whenever the ophthalmic artery was inappropriate for selective catheterization, the middle meningeal artery technique or balloon-method was used as an alternative. Consequently, the technical success rate of IAC (successful injection of chemotherapy into the ophthalmic artery) was recorded.

The chemotherapeutic agents included melphalan, carboplatin, and topotecan in the alternate delivery methods. Melphalan and carboplatin were used in the first session of IAC, whereas melphalan and topotecan in the second session. The dose of melphalan was  $\leq 0.5$  mg/kg, while that of topotecan and carboplatin was 1 mg and 20 mg, respectively. Each chemotherapeutic agent was diluted in 30 mL saline and delivered in a pulsatile manner over 30 min to minimize the laminar flow, stagnation, and loss of dose to peripheral vascular tributaries. Each session of IAC was conducted at a 4-week interval, and the necessity for further sessions was decided based on the tumor response.

### Patient follow-up

All the patients were examined 3 weeks after each treatment and every 3 months subsequently. The ophthalmic evaluation included an external examination and a pupil and motility evaluation. The systemic evaluation included an interval history and routine blood test. The follow-up data for each patient, including ocular adverse events, systemic adverse events, global salvage, and the largest basal dimension of the tumor were collected.

### Statistical analysis

Data were expressed as mean  $\pm$  SD and analyzed using SPSS 16.0 statistical software package (SPSS Inc., Chicago, IL, USA).  $P < 0.05$  indicated statistical significance.

## RESULTS

### Baseline characteristics

The present study retrospectively reviewed 24 eyes from 24 patients with advanced RB undergoing second-course IAC treatment post-recurrence after initial IAC.

Of these 24 patients, 11 (45.8%) were males, and 13 (54.2%) were females. The median age of the patients at the initial presentation was 17.1 months; 10 (41.7%) displayed unilateral, and 14 (58.3%) displayed bilateral disease. Of the bilateral cases, 2 had enucleation of the opposite eye, and the remaining 12 eyes showed a unilateral recurrence in the eye after initial IAC. According to IIRC, 24 eyes were classified as Group E (n=8, 33.3%) and Group D (n=16, 66.7%) at the initial examination. The initial IAC was delivered as primary therapy in 10 (41.7%) or secondary therapy in 14 (58.3%) cases after failure of intravenous chemotherapy in 6 cases and sequential treatment post-IVC in 8 cases. The second-course IAC was performed at a mean of 6.5 months (median 4, range 3–14 months) after the final cycle of initial IAC for recurrent main tumor in 19 cases (79.2%), recurrent subretinal seeds in 3 (12.5%), and recurrent vitreous seeds in 2 (8.3%). The characteristics of patients and eyes are shown in Table 1.

**Table 1** Characteristics of 24 eyes from 24 patients.

Parameters	Distribution
Gender	
Male	11 (45.8%)
Female	13 (54.2%)
Laterality	
Unilateral	10 (41.7%)
Bilateral	14 (58.3%)
Staging (eyes)	
Group D	16 (66.7%)
Group E	8 (33.3%)
Treatment before second-course IAC	
IAC	10 (41.7%)
IAC combined IVC	14 (58.3%)

## Treatment results

The treatment features are presented in Table 2. The second-course IAC was performed in 24 eyes, with a median of 3.2 sessions per eye (range, 2–4 sessions). Ten eyes (41.7%) were treated by IAC combined with a laser (range, 2–3 times), 3 eyes (12.5%) with cryotherapy (range, 1–3 times), and 2 eyes (8.3%) with a vitreous injection of melphalan (range, 1–2 times). The second-course IAC was technically successful in all cases using the ophthalmic artery in 20 (83.3%) or middle meningeal artery in 4 (16.7%) cases. No incidence of stroke and thromboembolic events were noted. Following second-course IAC, at the mean follow-up of 34 months (median 23, range 12–72 months), complete tumor and seed control were achieved in 15 eyes (62.5%). Eight eyes (33.3%) including 3 eyes of the IIRC Group D and 5 eyes of Group E required enucleation. Furthermore, 1 case of metastatic disease (4.2%) was recorded, who eventually died of brain metastasis after declining the treatment.

**Table 2** Treatment features in 24 eyes.

Parameters	Distribution
Number of second-course IAC cycles (sessions)	3.2 (2–4)
IAC technical success rate	100%
Global salvage rate	15 (62.5)
Metastatic rate	1 (4.2%)
Mortality rate	1 (4.2%)



**Figure 1.** Ocular adverse events after second-course intra-arterial chemotherapy.

**a:** An eye (IIRC group D) of a 1-year-old girl was treated via second-course IAC, and the left eye showed eyelid edema after two sessions of IAC.

**b:** An eye (IIRC group D) of an 8-month-old boy was treated via second-course IAC with the complications of eyelid swelling of the right eye and ipsilateral forehead erythema.

**c:** An eye (IIRC group E) of a 2-year-old boy was treated via second-course IAC with the ocular adverse event of enophthalmos of the right eye after second-course IAC in 3 sessions.

## Complications

Ocular adverse events included eyelid edema (n=12), ptosis (n=5), forehead erythema (n=5), enophthalmos (n=3) (Fig. 1), and cataract (n=2). The complications of eyelid edema and forehead erythema were diminished spontaneously. Although patients with complications of cataract recovered after surgery, those with enophthalmos did not undergo any treatment. None of the patients presented any systemic adverse events, such as stroke or sepsis. Also, no secondary neoplasms and technical complications were observed.

## DISCUSSION

Intra-arterial chemotherapy has been demonstrated as a remarkably potential treatment due to tumor control and relative lack of systemic side effects, especially advanced RB (11). According to the literature, primary IAC was successful in 72% of the eyes; however, secondary IAC was successful in 62% of the cases related to chemotherapy resistance from previous IAC exposure. (12). Herein, we specifically studied the second-course IAC in the treatment of recurrence of advanced tumor following initial IAC with the goal of evaluating the efficiency and complications of this repeat therapy. Consequently, 15 (62.5%) eyes showed complete control at a mean of the 34-month follow-up. Of these, 8 cases (33.3%) failed the therapy, and 1 case of metastatic disease (4.2%) eventually died of brain metastasis after refusing the treatment. None of the eyes developed new-onset large vessel compromise, and no child demonstrated systemic or brain effects.

Yousef et al. (13) found that the metastasis rate after IAC treatment was 2.1% as assessed by meta-analysis. However, the recurrence rate of advanced RB was as high as 29% (7) after IAC, and the majority of RB metastases occurred in the first year post-treatment (14). In 2013, Shields et al. (15) determined the efficacy of secondary IAC following primary IAC for patients with advanced RB and found that the global salvage rate was 57% at mean 2-year follow-up with no metastatic event. Therefore, to achieve the best effect without severe complications, unlike that in the study by Shields et al. (15), we did not use high doses of melphalan instead of using normal doses of melphalan by combination with carboplatin or topotecan in order to avoid the system toxicity of single drug chemotherapy and cross-resistance (8). In this study, the global salvage rate (62.5%) was lower than the reports of different studies with the global salvage rate of 83% using second-course IAC after initial IAC (16). We suspected that the slightly reduced control could be related to the advanced RB, and curing the tumor in a reduced-vascular site such as the subretinal space or vitreous cavity that might not receive adequate levels of chemotherapy is most challenging.

Metastatic RB has a high mortality rate despite the use of different treatments, such as neoadjuvant chemotherapy, surgery, or radiotherapy. A retrospective analysis (17) pre-

sented a 21-year clinical experience with metastatic extra-ocular RB patients; however, only 4.94% patients were alive, and some patients were deceased before further treatment. Thus, the doctors should continuously monitor and administer active treatment to these eyes, especially RB with a high risk of metastasis. In the present study, the patient with metastasis died during the follow-up period after refusing further treatment as it was cost-ineffective. Owing to the economic constraints in China, some of the families with RB children harboring tumor metastasis had negative treatment attitude or refused further treatment.

Additionally, there are few reports of enophthalmos and cataract after IAC. Thus, it was hypothesized that vascular insult to the long posterior ciliary artery might have resulted in chronic changes that led to ischemia, iris atrophy, and eventually enophthalmos (18). The crystalline lens is one of the most radiosensitive tissues in the body and accumulated irradiation doses by IAC sessions could increase the probability of cataract development in the treated eye. The current study found slightly higher incidence rates of enophthalmos and cataract at 12.5% and 8.3%, respectively. Thus, repeat IAC therapy was hypothesized to increase the possibility of vascular damage and the incidence of cataracts. Therefore, second-course IAC was not suitable for all patients with RB. Those with multiple sessions of IAC treatment in advanced disease and high-risk features of optic nerve invasion should be considered for enucleation and adjuvant systemic chemotherapy.

Nevertheless, this study has several limitations such as retrospective design and the relatively small sample size. Also, the additional recurrences or complications may occur with a prolonged duration of follow-up. Thus, a prospective study with a large patient population and long-term follow-up is warranted for additional guidance for clinical treatment.

In summary, second-course IAC is a potential alternative to enucleation in children with advanced retinoblastoma, who fail the initial course of IAC. However, we recommend that patients with advanced retinoblastoma should be managed by doctors at experienced centers such that all alternatives can be considered before enucleation.

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