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ARTICLE

Outcome of salvage intra-arterial chemotherapy for recurrent retinoblastoma

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PURPOSE: To examine the outcome of salvage intra-arterial chemotherapy (IAC) for patients with recurrent retinoblastoma after the initial course of IAC and determine the factors influencing clinical outcome.

METHODS: A total of 73 eyes of 71 patients with recurrent retinoblastoma undergoing salvage IAC after initial successfully IAC between May 2014 and May 2019 were retrospectively reviewed for clinical outcomes. Ocular survival and progression-free survival were used to examine the efficacy of salvage IAC. The factors influencing clinical outcomes were determined using univariate and multivariate analyses.

RESULTS: The salvage IAC was delivered at mean 9.4 months (median 7, range 2.1–38.3 months) following the last cycle of initial IAC. 86.5% (64/73) eyes relapsed 16 months after the initial IAC. After the salvage IAC, 57 eyes (78.1%) were salvaged, and no further-line therapies were required for 36 eyes (49.3%). The 2-year Kaplan–Meier ocular survival and progression-free survival estimates after salvage IAC were 66.4% (95% CI, 31.5–42.1%) and 38.2% (95% CI, 17.8–28.8%), respectively. Univariate and multivariate analyses showed that the ocular survival and progression-free survival after salvage IAC were significantly associated with the history of vitreous seeds ($p = 0.02$ and $p = 0.03$, respectively).

CONCLUSION: Salvage IAC is effective for the management of recurrent retinoblastoma after the initial successful IAC. Eyes with a history of vitreous seeds in the course of the disease are more likely to relapse and with worse ocular survival. A close follow-up strategy is imperative to treat the recurrent tumour after salvage IAC.

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INTRODUCTION

Retinoblastoma is the most common primary intraocular tumour in children [1]. Multiple treatment modalities have been developed to treat retinoblastoma, including external beam radiotherapy (EBR), intravenous chemotherapy (IVC), and focal techniques [2]. However, the efficacy of these managements for advanced disease is not satisfactory. Over the past decade, Intra-arterial chemotherapy (IAC), also known as ophthalmic artery chemosurgery (OAC), has emerged as the first-line management option in advanced retinoblastoma. This technique is commonly adopted as primary therapy for advanced retinoblastoma, and it is also widely used as secondary therapy after the failure of systemic chemotherapy [3, 4]. With IAC therapy, group B and C eyes have an excellent eye salvage rate, ranging from 95% to 100%, similar to IVC. Excitingly, eye salvage rate in group D and group E can achieve 94% and 36%, respectively [5].

Nevertheless, about 24% of the disease recurred after the initially successful IAC treatment [6]. For these eyes, enucleation is often the main alternative. In cancer treatment, salvage chemotherapy refers to chemotherapy given to a patient when other options are exhausted [7, 8]. In our institution, re-employ a second-course IAC as a salvage therapy is another option for patients who had recurrent tumour after the first course of IAC. Herein, we report the outcome of our usage of salvage IAC for eyes had recurrent tumours after initial IAC during the intravitreal chemotherapy era.

MATERIALS AND METHODS

Patients

This is a single-institution, single-arm retrospective study approved by the Institutional Review Board of Xin Hua Hospital affiliated with Shanghai Jiao Tong University School of Medicine. The study was conducted in accordance with the Declaration of Helsinki. Informed written consent was obtained from the adult patients or parents/guardians of underage patients. Medical records were reviewed for all patients with retinoblastoma who received salvage IAC at the time of their recurrence/progression after having completed one IAC course as a primary or secondary treatment at our institution from May 2014 to May 2019.

Patient data included age, gender, laterality, age at the start of both initial and salvage IAC, previous IVC history before the initial IAC. Tumour features included International Classification of Retinoblastoma grouping, vitreous seeds status, and types of recurrent tumour after initial IAC. IAC treatment data included the number of infusions, drug doses both in initial and salvage IAC.

All patients underwent examinations under general anaesthesia prior to treatment with salvage IAC, including anterior segment evaluation, fundus evaluation with indirect ophthalmoscopy. Clinical findings were documented via fundus photography using RetCam (Clarity, Pleasanton, CA,

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USA), B scan ultrasonography, and, as needed, fluorescein angiography and optical coherence tomography. As with the initial IAC, the treatment interval was also 3 or 4 weeks during the course of salvage IAC. The number of IAC infusions depended on tumour response.

Intra-arterial chemotherapy

The catheterisation procedure of the initial and salvage IAC was the same, all performed by the interventional neuroradiologists under general anaesthesia. Intravenous heparin (75 IU/kg) was used for anticoagulation. The femoral artery was punctured with a 5-French (5-F) arterial sheath, and the ipsilateral internal carotid artery is catheterised under fluoroscopic guidance. Serial arteriograms helped visualise the ocular and cerebral vasculature to obtain the best approach to the ophthalmic artery from the internal carotid artery. The ophthalmic artery was catheterised with a 1.5-F microcatheter using fluoroscopy and road mapping, and then an angiogram of the ophthalmic artery was taken. Chemotherapeutic agents were diluted in 30 ml of 0.9% saline and administrated in a pulsatile fashion over 30 min to achieve homogeneous drug delivery. In our centre, we adopt the three-drug protocol for both the initial and salvage IAC treatment, which is also currently accepted by many other centres [3]. The chemotherapeutic agents used in the protocol include melphalan (3–7.5 mg), topotecan (1 mg), and carboplatin (30–65 mg). The specific dose of the drugs is related to the patient's age and severity of the disease. The dosage of melphalan should be less than 0.5 mg/kg. For patients treated with bilateral retinoblastoma simultaneously, the catheter was retracted to the aorta and guided into the ophthalmic artery of the other eye using the same procedure.

Statistical analysis

Kaplan–Meier analysis was performed to estimate ocular survival and ocular progression-free survival utilising Prism (GraphPad Software, La Jolla California USA, www.graphpad.com). Progression of disease was defined as recurrent cases that required further-line therapies such as intravitreal melphalan injection, EBR, additional IAC, or enucleation. Survival estimates were compared in terms of patient data, tumour features, and IAC treatment data with univariate and multivariate analyses. Univariate analysis between curves was done by log-rank test. Multivariate analysis was done by Cox regression using SPSS 19.0 statistical software package (SPSS Inc., Chicago, IL, USA). The level of significance was $p < 0.05$.

RESULTS

A total of 73 eyes of 71 people were included in the study. Table 1 summarises the demographic characteristic of the patients. Of the bilateral cases, 4 had enucleation of the fellow eye. Among the 39 eyes (53.4%) treated with initial IAC as secondary therapy after failure of intravenous chemotherapy, five eyes discontinued intravenous chemotherapy because of uncontrolled tumour or recurrence. Twenty-six (35.6%) eyes of our cohort had a history of vitreous seeds at a certain point in the course of the disease and received treatment with intravitreal melphalan injection.

The salvage IAC was delivered at mean 9.4 months (median 7, range 2.1–38.3 months) following the last cycle of initial IAC. 86.5% (64/73) eyes relapsed 16 months after the initial IAC. Eyes treated with a median of 3 cycles during the initial IAC course and a median of 2 cycles during the salvage IAC course. The mean follow-up time was 15.9 months (median 13.4, range 3.4–49.7 months) from the beginning of the salvage IAC. The salvage IAC was technically successful in all eyes. Tumour and seed control were achieved in all cases after the course of salvage IAC. During the follow-up time, no further-line therapies were required for 36 eyes (49.3%), such as intravitreal melphalan injection or IAC (Fig. 1). Tumour recurred in the remaining 37 eyes (50.7%) despite the salvage IAC, with 89.2% (33/37) recurrence happened within 12 months. Twenty-one of these eyes were salvaged with further-line therapies, while sixteen received enucleation. The supplementary table describes the treatment and outcome characteristics of each eye.

The 2-year Kaplan–Meier ocular survival and progression-free survival estimates were 66.4% (95% CI, 31.5–42.1%) and 38.2% (95% CI, 17.8–28.8%), respectively. Univariate analysis by log-rank test revealed that eyes with history of vitreous seeds were significantly associated with shorter ocular survival and progression-free survival. In addition, unilateral eyes and eyes without previous IVC before initial IAC were associated with worse ocular survival (Table 2). Multivariate Cox proportional hazard analyses of univariate factors are shown in Table 3. It turned out only history of vitreous seeds was significant independent factors for worse ocular survival and progression-free survival ($p = 0.02$ and $p = 0.03$, respectively). 2-year Kaplan–Meier ocular survival estimates after salvage IAC were 84.1% for eyes without history of vitreous seeds and 43.6% for eyes with history of vitreous seeds. 2-year Kaplan–Meier progression-free survival estimates after salvage IAC were 45.9% for eyes without history of vitreous seeds and 25.6% for eyes with history vitreous seeds (Fig. 2).

Table 1. Characteristics of 73 eyes in the study.

Characteristic	Distribution
Gender, no. (%)	
Males	38 (52.1)
Females	35 (47.9)
Mean age, mean, mos	
At initial IAC	26.1 (6.1–97.2)
At second course of IAC	37.4 (10.3–102.2)
Laterality, no. (%)	
Unilateral	42 (57.5)
Bilateral	31 (42.5)
International classification, no. (%)	
C	2 (2.7)
D	48 (65.8)
E	23 (31.5)
Treatment before initial IAC, no, (%)	
None	34 (46.6)
Systemic chemotherapy	39 (53.4)
Reasons for salvage IAC	
Solid tumour	45 (61.6)
Subretinal seeds	18 (24.7)
Vitreous seeds	10 (13.7)

DISCUSSION

It is well demonstrated that the globe salvage rate of IAC was higher than that of IVC, especially for advanced retinoblastoma [9–11]. IAC is now considered as a standard option for the management of advanced retinoblastoma as both a primary and a secondary treatment [4]. However, there was no significant difference in the recurrence rate between IAC and IVC in a recent meta-analysis comparing IVC with IAC [12]. If the tumour recurred after IAC and cannot be managed by focal treatment, then the conventional practice is enucleation. This is very cruel for patients with bilateral tumours, while the fellow eye has been enucleated. Also, in China, some families are often reluctant to remove the eyes of children for some superstitious reasons.

In this report, we described the outcome of salvage IAC for eyes had recurrent tumour after initially successful IAC. A total of 73 eyes were included in our study, and 57 eyes (78.1%) survived at the end of the follow-up. 2-year Kaplan–Meier ocular survival estimates of our cohort were 66.4%, which means that salvage IAC can save more than half the eyes that theoretically demand enucleation. It should be noted that during the follow-up period, about half of the eyes had recurrence after salvage IAC, which required further-line therapies. 2-year progression-free survival estimates were 38.2%.

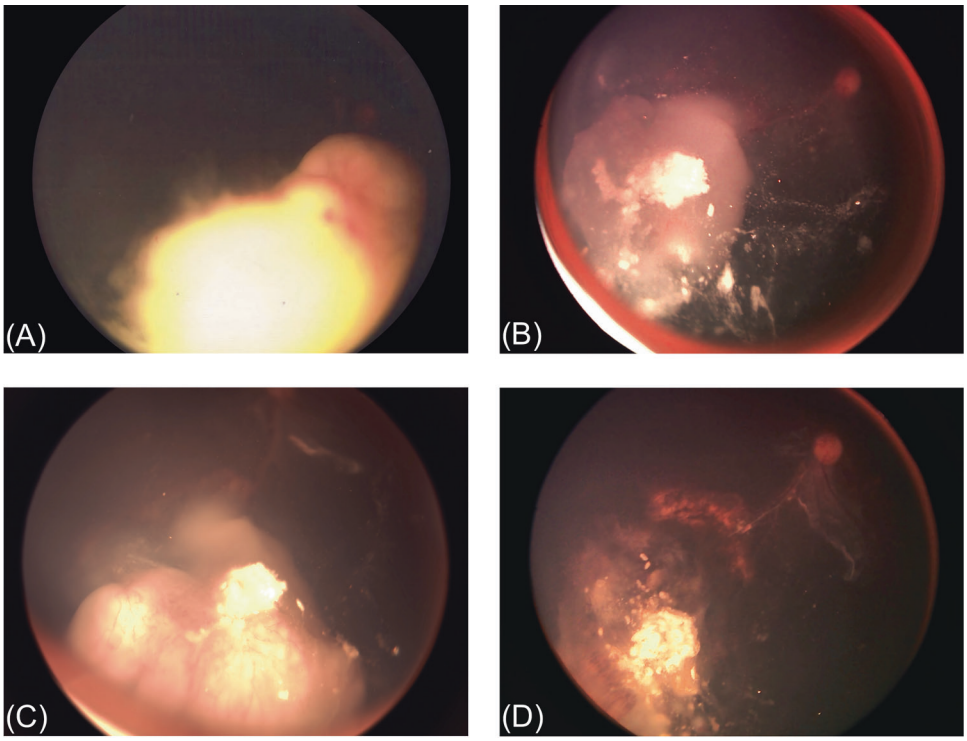

Fig. 1 Recurrent tumor control was achieved by salvage IAC. A female child (Patient No. 5) was diagnosed with group D retinoblastoma of the left eye at the age of 24-month-old (**A**). After the treatment of initial IAC, the main tumour was regressed to a translucent fish-flesh appearance mixed with a calcified component (**B**). After an 8.1-month follow-up after the initial IAC, a solid tumour was progressed beneath to the regressed tumour (**C**). After the management of salvage IAC, the recurrent tumour regressed to a flat scar and without other recurrences during the follow-up period (**D**).

Table 2. Factors associated with survival estimates by univariate analysis.

Characteristics		No.	*p* value	
			Ocular survival	Progression-free survival
Sex	Male	38	0.97	0.45
	Female	35		
Laterality	Unilateral	42	**0.04**	0.54
	Bilateral	31		
Classification	Group D	48	0.65	0.15
	Group E	23		
Previous IVC history before initial IAC	Yes	39	**0.02**	0.54
	No	34		
Reasons for the second course of IAC	Solid tumour	45	0.37	0.22
	Subretinal seeds	18		
	Vitreous seeds	10		
History of vitreous seeds	Yes	26	**0.01**	**0.03**
	No	47		
Infusion cycles of initial IAC	<3	18	0.42	0.27
	≥3	55		
Infusion cycles of the second course of IAC	<2	15	0.39	0.65
	≥2	58		
Interval between two IAC	<7	36	0.26	0.13
	≥7	37		
Increased drug dose	Yes	42	0.6	0.22
	No	31		

Bold values indicate statistical significance $p < 0.05$.

Table 3. Factors associated with survival estimates by multivariate Cox regression analysis.

	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Laterality	–	0.11	–	0.98
Previous treatment History	–	0.07	–	0.2
History of vs	3.49 (1.21–10.01)	**0.02**	2.02 (1.06–3.85)	**0.03**

Bold values indicate statistical significance $p < 0.05$.

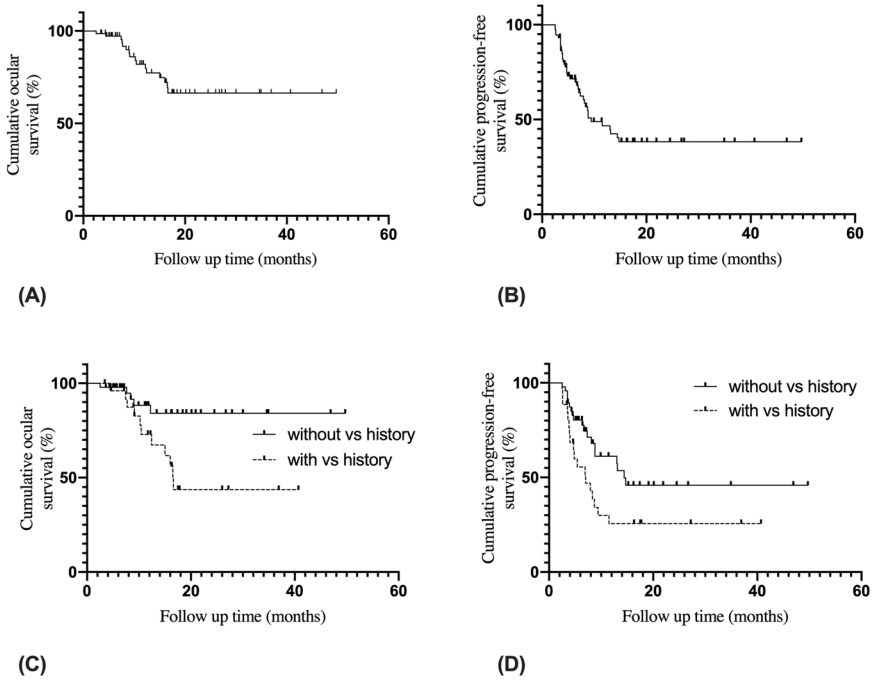

Fig. 2 Survival analysis of patients in our cohort. 2-year Kaplan–Meier curves of all eyes for (**A**) ocular survival and (**B**) progression-free survival. Eyes with a history of vitreous seeds had significant worse (**C**) ocular survival and (**D**) progression-free survival.

This suggests that despite the improved survival rate, a close follow-up strategy is still essential for the treatment of recurrent disease.

To the best of our knowledge, only two studies have reported on the treatment efficacy of the second course of IAC [13, 14], which was termed as rescue IAC by Shields et al. Compared with these two reports, we have more sample sizes, and all cases were treated during the intravitreal chemotherapy era. Francis et al. reported that 17 (58%) eyes required second course of IAC due to the recurrence of vitreous seeds and were associated significantly with worse ocular survival [13]. In our study, only 10 (13.7%) eyes received the salvage IAC for the reason of recurrent vitreous seeds. Compared to other factors, there were no significant associations found between recurrent vitreous seeds and worse ocular survival or progression-free survival. The difference in this result is most likely because our cases were treated in the era of intravitreal chemotherapy, and with this approach, most of the eyes with vitreous seeds can be saved without additional IAC therapy [15–17].

However, we found history of vitreous seeds in the course of disease was the independent variable associated significantly with both worse ocular survival and progression-free survival through the univariate and multivariate analyses. In our report, a total of 39 (53.4%) eyes had vitreous seeds at some point in the course of the disease and were treated with intravitreal injections. It is unclear how the history of vitreous seeds is a risk factor for disease progression. We suspect that despite the effectiveness of intravitreal melphalan injection, one that also might have microscopic vitreous seeds and are at risk for recurrence. Thus, eyes with history of vitreous seeds should be carefully documented and followed up closely.

As can be seen from the progression-free survival curves, almost all of the disease progression occurred during the first 16 months of follow-up, and after 16 months it ended with an extended plateau - a nearly flat line. This may indicate the first 16 months of salvage IAC is a high-risk period of relapse, and the disease gradually stabilises after 16 months. However, this requires a larger sample size and a longer follow-up time to determine.

In summary, salvage IAC for eyes failed in the initial course of IAC can achieve a good ocular survival rate. However, a close follow-up strategy is essential for the further-line treatment of recurrent disease. In eyes with history of vitreous seeds, the disease is more prone to recurrence and with worse ocular survival.

Summary

What was known before

- Intra-arterial chemotherapy is currently the first-line treatment for retinoblastoma.
- Enucleation is the main alternative therapy for recurrent retinoblastoma after initial course of intra-arterial chemotherapy.

What this study adds

- We explore the outcome of reusing IAC as a salvage therapy for recurrent retinoblastoma. The outcome showed it is an

effective option for eyes that failed in the initial course of IAC.
- History of vitreous seeds was the independent factor associated significantly with worse ocular survival despite the salvage intra-arterial chemotherapy.

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AUTHOR CONTRIBUTIONS

JL was responsible for designing the review protocol, writing the protocol and article, conducting the search, extracting and analysing data, interpreting results, updating reference lists; CJ was responsible for the operation of intra-arterial chemotherapy, extracting and analysing data; XH was responsible for the operation of intra-arterial chemotherapy and provide clinical data; TL was responsible for the collection and sorting of information; JL was responsible for designing the review protocol and screening potentially eligible studies; PZ contributed to the design of the review protocol and provided feedback on the report; XJ was responsible for the provision of clinical data and designing the review protocol.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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