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Intra-arterial chemotherapy for retinoblastoma: Experience from the pediatric ophthalmology referral center in Malaysia with literature review

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Abstract:

PURPOSE: We aimed to analyze our 4-year experience of intra-arterial chemotherapy (IAC) for retinoblastoma (RB) and to examine the tumor response, globe salvage, mortality, and safety profile of IAC in the Malaysian profile.

MATERIALS AND METHODS: This was a retrospective, interventional case series. A total of 22 eyes of 20 patients with RB who underwent IAC using melphalan and topotecan from January 2018 to December 2021 in Hospital Kuala Lumpur were retrospectively reviewed. Tumor response, globe salvage, mortality, and safety profile of IAC were compared based on the International Classification of Retinoblastoma.

RESULTS: The mean patient age at IAC was 21.3 months. An overall globe salvage rate of 63.6% was observed: more specifically, 100% for Group A, 75% for Groups B and C, 66.7% for Group D, and 42.9% for Group E. Poor tumor response after IAC was significantly associated with a lesser chance of globe salvage (P = 0.045). The overall rate of good tumor response following IAC was 77.3%. Specifically, rates of good tumor response in each group were 100%, 75%, 75%, 83.3% and 71.4% in group A, B, C, D and E, respectively. The mortality rate was 5%. Complications (per-catheterization) included cerebral infarct (2.2%), oxygen desaturation (2.2%), vomiting (26.1%), periorbital edema (8.8%), ptosis (6.5%), fever, femoral hematoma, and hyperpigmentation over lid (4.4% each).

CONCLUSION: Four-year experience showed that IAC is a safe and effective method for RB management. Patients with a poor response after IAC may have a lower chance of globe salvage. Careful patient selection is of utmost importance to achieve the best outcome in a setting of limited health-care resources.

Keywords:

Developing nation, globe salvage, intra-arterial chemotherapy, retinoblastoma

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Introduction

Retinoblastoma (RB) is the most common intraocular malignancy among children and is considered fatal if left untreated. Management aims to prevent mortality, then globe salvage, and finally to preserve vision as much as possible.

Multiple treatment options have been used in managing this fatal malignancy, including enucleation, intravenous chemotherapy, external beam radiation, cryotherapy, plaque brachytherapy, and laser photocoagulation. Intra-arterial chemotherapy (IAC) was first introduced by Yamane *et al.* by infusing melphalan into the ipsilateral carotid artery

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of the eye with RB.[1] Then, Abramson *et al.* began to selectively inject the chemotherapeutic agent into the ophthalmic artery (OA) in 2008.[2] This technique soon becomes a popular technique among developed countries due to its promising result and good safety profile.[3,4]

However, the IAC procedure requires an expert interventional radiologist. Hence, only limited literature reported IAC among developing nations.[5,6] We hereby report the 4-year outcome of IAC at Hospital Kuala Lumpur, the national referral center for RB in Malaysia.

Materials and Methods

This was a retrospective, nonrandomized, noncomparative, interventional case series; a total of 22 eyes of 20 RB patients who underwent the IAC procedure from January 1, 2018, till December 31, 2021, in Hospital Kuala Lumpur were included. This research adhered to the tenets of the Declaration of Helsinki, and ethical approval was obtained from the Medical Research and Ethics Committee of the Ministry of Health Malaysia (NMRR ID-22-01505-0QQ) patient consent.

All patients were examined by pediatric ophthalmology consultants. Fundus photography was captured by Retcam® imaging (Massie Industries, Dublin, CA, USA), and clinical data were extracted from electronic medical records. All patients underwent detailed ocular examinations under general anesthesia. Eyes were classified using the International Classification of Retinoblastoma (ICRB). Bilateral RB that received IAC on both eyes was analyzed separately. Factors of interest include age, race, gender, diagnosis, laterality, ICRB stage, type of chemotherapeutic agents, number of IACs attempted and success, IAC routes, treatment given before IAC, indication of IAC, tumor response post-IAC, procedure-related complications, globe salvage, and mortality.

Indication of IAC was classified into primary (treatment-naïve tumor) and secondary (progressive, persistent, and recurrent tumor). Progressive tumor was defined as worsening of tumor despite the commencement of intravenous chemotherapy with or without other treatment modalities such as cryotherapy, laser photocoagulation, periocular chemotherapy, or intravitreal chemotherapy. Persistent tumors include nonregressing main tumor mass and the presence of subretinal seed or vitreous seed despite maximum treatment. Recurrent tumors were defined as the re-appearance of seed or increased tumor size after initial signs of tumor regression.

IAC was performed by interventional radiologists under general anesthesia. The technique was similar to other reported studies.[5,6] The femoral artery was punctured and a 4-Fr pediatric arterial catheter was inserted under ultrasonographic guidance. A 4-Fr headway catheter with guidewire was then guided to the ipsilateral internal carotid artery (ICA). There were 2 possible routes of cannulation, first path was ICA to OA; second route was external carotid artery to middle meningeal artery and eventually enter into OA. The route differs according to anatomical variation. After the accomplishment of road mapping, a microcatheter was used to catheterize the OA [Figure 1]. After vascularization to the globe and flow were verified, the chemotherapeutic agent was delivered directly into the OA. The dosage of melphalan was adjusted to age: 2.5 mg (3–6 months old), 3 mg (6–12 months old), 4 mg (1–3 years old), and 5 mg (>3 years old). The topotecan dosage was also adjusted to age: 0.4 mg (3–6 months old), 0.5 mg (6–12 months old), 0.75 mg (1–3 years old), and 1 mg (>3 years old).

Outcomes of interest included procedure-related complications, tumor response, and mortality. Tumor response was observed on the following examination under anesthesia 3 weeks after IAC. It was divided into complete response (no degree of residual viable tumor), partial response (some degree of residual viable tumor), and progression (tumor advancement in size and seedings).

Statistical analysis

All the data were analyzed by using the Statistical Package for Social Sciences version 25.0 (SPSS, Inc., Chicago, IL, USA). Descriptive data were done to describe the demographic of the population. Categorical data were expressed in frequency and percentage, and numerical data were expressed in terms of mean and standard deviation (if normally distributed) or median with interquartile range (if abnormally distributed). For inferential analysis, all the categorical data were analyzed with Chi-square test while numerical data were analyzed with independent *t*-test. Fisher's exact test was used if the criteria for Chi-square test were not met. $P < 0.05$ was considered statistically significant.

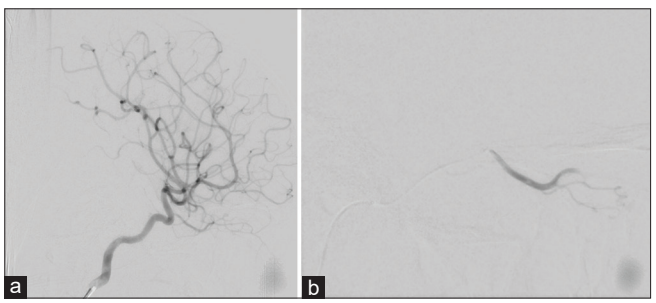

Figure 1: (a) Angiogram was performed with the catheter at the internal carotid artery, demonstrating its branches including the ophthalmic artery. (b) Superselective ophthalmic artery angiogram. These images were done with digital subtraction angiography, in which all the other structures were extracted and only the contrast within the blood vessel was shown

Results

In total, 22 eyes of 20 patients with RB were treated with IAC in 4 years at our center. Patient demographics are displayed in Table 1. The mean patient age at IAC was 21.3 months (median, 19 months; range 7 to 63 months).

Among 22 eyes, 1 eye (4.5%) received melphalan only, and the other 21 eyes (95.5%) received both melphalan and topotecan as their chemotherapeutic agents. IAC was administered as the second line of therapy in 17 eyes (77.3%) and as primary therapy in 5 eyes (22.7%). All 5 patients who received IAC as primary therapy were unilateral RB; all of them are Group C or above.

There were total 51 cannulations performed on the 22 eyes (2.32 attempts each eye on average). Total 46 successful cannulations out of the 51 cannulations gave us 90.2% of success rate. Three eyes contributed to the 5 failed cannulations and all of them are Group D or Group E. All the eyes that received IAC therapy are listed in Table 2 and were classified according to the ICRB as Group A (n = 1, 4.5%), Group B (n = 4, 18.2%), Group C (n = 4, 18.2%), Group D (n = 6, 27.3%), and Group E (n = 7, 31.8%).

The outcome of IAC showed that 18.2% of eyes had complete regression of the tumor. Thirteen eyes (59.1%) had partial response toward IAC [Figure 2]. The remaining 5 eyes (22.7%) manifest tumor progression despite IAC. We classified complete response and partial response into good response and plotted a bar graph to assess the overall IAC response in each group. Overall, 77.3% of the eyes have a good response after IAC therapy [Figure 3].

Table 1: Patient demographics (n=20 patients)

Characteristic	n (%)
Sex	
Male	12 (60)
Female	8 (40)
Laterality	
Unilateral	7 (35)
Bilateral	13 (65)
Ethnicity	
Malay	15 (75)
Chinese	5 (25)
Mean age of diagnosis (months)*	11.2 (5.5; 1-63)
Mean age of IAC (months)*	21.3 (19; 7-63)
Mean duration of follow-up (months)*	30.7 (25; 10-89)

*Data are expressed as mean (median; range). IAC=Intra-arterial chemotherapy

Table 2: Summary of clinical details, treatment outcomes, and safety profile of intra-arterial chemotherapy according to the International Classification of Retinoblastoma

	A, n (%)	B, n (%)	C, n (%)	D, n (%)	E, n (%)	Total, n (%)
Number of eyes	1	4	4	6	7	22
Number of successful cannulations	2	9	6	17	12	46
Mean IAC per eye	2	2.25	1.5	2.83	1.71	2.09
Number of failed cannulations	0	0	0	4 (23.5)	1 (8.3)	5 (10.9)
Indication						
Primary treatment	0	0	1 (25)	2 (33.3)	2 (28.6)	5 (22.7)
Progression	0	1 (25)	2 (50)	3 (50)	0	6 (27.3)
Recurrent	1 (100)	2 (50)	0	0	0	3 (13.6)
Persistent	0	1 (25)	1 (25)	1 (16.7)	5 (71.4)	8 (36.4)
Outcomes						
Complete response	1 (100)	1 (25)	0	1 (16.7)	1 (14.3)	4 (18.2)
Partial response	0	2 (50)	3 (75)	4 (66.7)	4 (57.1)	13 (59.1)
Progression	0	1 (25)	1 (25)	1 (16.7)	2 (28.6)	5 (22.7)
Intra- and post-IAC complications						
Cerebral infarct	0	0	0	0	1 (8.3)	1 (2.2)
Oxygen desaturation	0	0	0	1 (5.8)	0	1 (2.2)
Vomiting	1 (50)	2 (22.2)	1 (16.7)	5 (29.4)	3 (25)	12 (26.1)
Fever	0	0	0	2 (11.8)	0	2 (4.4)
Periorbital edema	1 (50)	1 (11.1)	0	1 (5.8)	1 (8.3)	4 (8.8)
Right femoral hematoma	0	1 (11.1)	0	1 (5.8)	0	2 (4.4)
Hyperpigmented patch over lid	0	0	1 (16.7)	1 (5.8)	0	2 (4.4)
Ptosis	0	0	0	2 (11.8)	1 (8.3)	3 (6.5)
Globe salvage						
Yes	1 (100)	3 (75)	3 (75)	4 (66.7)	3 (42.9)	14 (63.6)
No	0	1 (25)	1 (25)	2 (33.3)	4 (57.1)	8 (36.4)
Mortality						
Yes	0	0	0	1 (16.7)	0	1 (5)
No	0	4 (100)	3 (100)	5 (83.3)	7 (100)	19 (95)

IAC=Intra-arterial chemotherapy

The complications related to the IAC procedure are listed in Table 2. The main complications included vomiting (26.1%), periorbital edema (8.8%), and ptosis (6.5%). One patient developed oxygen desaturation during the IAC procedure and resolved uneventfully. The most devastating complication in this study was cerebral infarct; one patient (2.2%) encountered a left-sided focal seizure post-IAC. Computer tomography (CT) of the brain revealed an acute right middle cerebral artery territory infarct. This patient eventually recovered with no residual weakness.

Globe salvage is one of the important outcomes to be observed among RB patients. Of 22 eyes, globe salvage was maintained in 14 eyes (63.6%), with 100%, 75%, 75%, 66.6%, and 42.9% in ICRB Groups A, B, C, D, and E, respectively (P = 0.788). Indications for IAC therapy showed no significant difference in terms of globe salvage rate. The group that showed disease progression post-IAC therapy was associated with a lower globe salvage rate compared to eyes that have a complete or partial response (P = 0.045). There was one patient demised in this study due to pelvis metastasis. However, enucleations have no significant relationship with mortality in this study (P = 0.121) [Table 3].

Discussion

IAC for RB has been extensively studied in developed countries with numerous published articles. It requires high technical skills and specialized facilities, which limits its availability in developing nations. Hence, there is a paucity of data in terms of outcomes of IAC in developing nations. Our study aims to supply more information on IAC outcomes from the developing region; currently, our center is the only facility in Malaysia that provides IAC for intraocular RB.

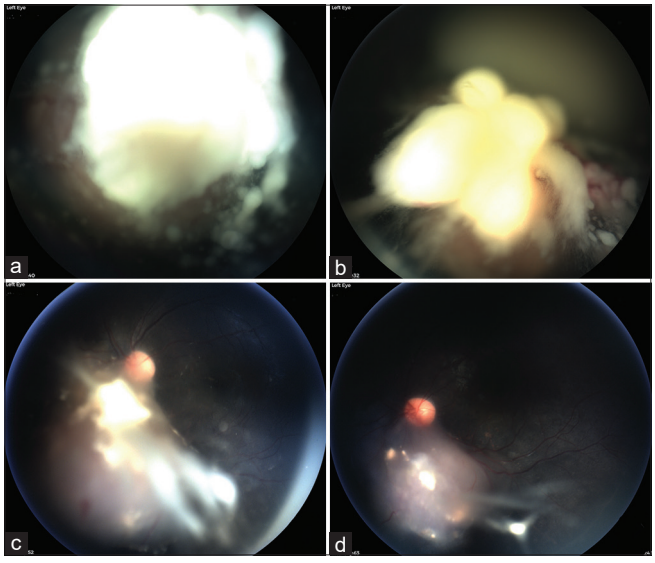

Figure 2: (a) Unilateral Group D intraocular retinoblastoma appearance during the first EUA, large calcified mass with vitreous seeding. (b) After 1 cycle of IAC, the calcified mass reduced in size with vitreous seeding. (c) After 3 cycles of IAC, the tumor shrank further with optic disc exposed and less vitreous seeding. (d) After 5 cycles of IAC, mass reduced to 4-disc diameter in size with vitreous veil anteriorly. EUA: Examination under anesthesia. IAC: Intra-arterial chemotherapy

At our institute, we started IAC for intraocular RB in 2014. Initially, our center only commenced IAC as secondary therapy and the cannulation success rate was around 71.8%.[5] We started IAC as primary treatment for unilateral RB in 2019 supported by promising outcomes reported from developed nations.[3,4,7,8] Twenty-two point seven percent of our patients were treated with IAC as primary therapy with a globe salvage rate of 40%. Eighty percent of the eyes that received IAC as primary therapy were Group D or E. One of the reasons was most of our patients presented to us at advanced stages. On top of that, all these patients suffered from unilateral advanced RB, and without primary IAC these eyes would have been enucleated. Although the globe salvage rate among the primary IAC group is slightly lower compared to developed nations (43%–100%)[4,9-12], most of the eyes enucleated in our primary IAC therapy group were Group E. Besides the cannulation success rate increased from 71.8% in 2018 to 89.1% due to the improvement of skills and more practices along the learning curve.[5]

The globe salvage rate among the secondary IAC therapy group was 70.6%; this result was comparable with other published data (50%–100%).[3,4,6,9,10,12,13] Most papers showed a higher globe salvage for eyes that received IAC as primary treatment compared to eyes that

Table 3: Globe salvage rate

	Globe salvage		*P*
	Yes	No	
Group			
A	1 (100)	0	0.788
B	3 (75)	1 (25)	
C	3 (75)	1 (25)	
D	4 (66.6)	2 (33.4)	
E	3 (42.9)	4 (57.1)	
Indication			
Primary treatment	2 (40)	3 (60)	0.612
Progression	5 (71.4)	2 (29.6)	
Recurrent	1 (50)	1 (50)	
Persistent	6 (75)	2 (25)	
Treatment			
IVT/periocular chemo + IAC	8 (57.1)	6 (42.9)	0.649
IAC only	6 (75)	2 (25)	
Outcomes			
Complete response	4 (100)	0	0.045
Partial response	9 (69.2)	4 (30.8)	
Progression	1 (20)	4 (80)	
Mortality			
Yes	0	1 (100)	0.121

IVT=Intravitreal, IAC=Intra-arterial chemotherapy

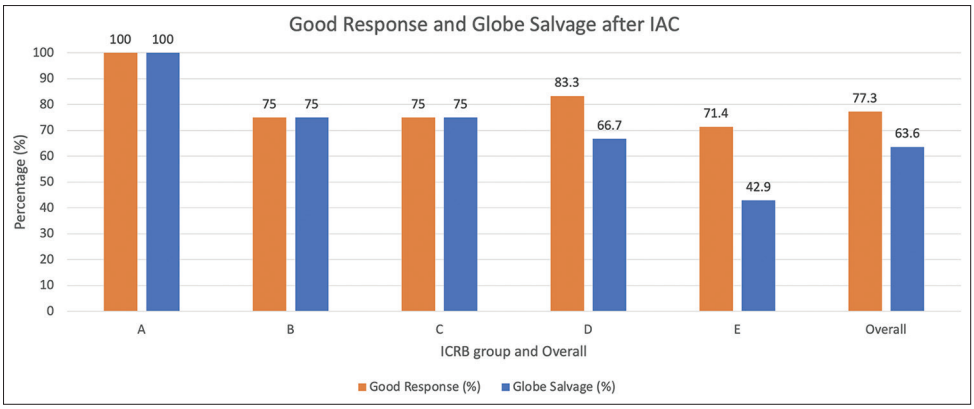

Figure 3: Bar chart showing good response (combination of complete response and partial response) and globe salvage rate after IAC therapy according to the ICRB group. IAC: Intra-arterial chemotherapy, ICRB: International Classification of Retinoblastoma

received secondary IAC therapy. However, our results revealed a lower globe salvage rate among the primary IAC therapy group (40%) compared to the secondary IAC therapy group (70.6%). This discrepancy might be explained by inclusion bias, in which the majority of the eyes in the primary IAC therapy group were Group D or E (80%), while only 46.2% of the eyes in the secondary IAC therapy group were Group D or E.

In Malaysia, our RB patients presented to healthcare provider at a rather advanced stage. Menon *et al* reported that 59.1% of Malaysian RB patients presented as Group D or Group E.[14] Our globe salvage rate based on ICRB classification echoed data from other studies. The globe salvage rate for Groups A to C was 75%–100%, which supports the efficacy of IAC among our populations. Group D had a slightly lower globe salvage rate of 66.6% compared to 86% reported by Shields *et al*.[4] The reason could be the complexity of management for Group D RB which includes intravitreal and periocular chemotherapy. All these variables were not taken into consideration while we analyzed the dataset, as the number is too small compared to other major centers in the US. In an attempt to analyze whether intravitreal or periocular chemotherapy had any impact on the globe salvage rate in our center, the result was not significant (P = 0.649). Our globe salvage rate in Group E eyes was 42.9%, which is comparable with other studies (30%–90%) and slightly higher than our Thailand peers.[3,4,6,15-17]

Initial tumor responses post-IAC were important data and likely to serve as a predictor for potential treatment failure and eventually enucleation. Progression of RB after IAC was associated with enucleation (P = 0.045). Eyes which encountered progression after IAC might not be a good candidate to continue the IAC treatment modality, and other alternatives should be sought earlier for this group of patients. Further study is required to figure out the exact duration and cycles of IAC to patients that responded poorly to IAC, before we pronounced them as treatment failure. The risk of distant metastasis always haunts us when we were balancing the risk and benefit of globe salvage in patients with poor responses to IAC. Eyes that showed partial response will receive further IAC treatment until the tumor regressed completely. In cases that tumor could not be eliminated completely, other treatment modalities will be started depending on the stages of RB, such as systemic chemotherapy or enucleation in advance disease.

The risk of metastatic deaths in RB in countries with advanced IAC facilities was reported as <1% over 10 years (3 out of 1139 patients).[18] From our literature review [Table 4], the mortality rate reported ranges around 1%–8%.[6,17,19-21] Most of the patients succumbed due to trilateral RB or metastatic disease. IAC therapy in our center is relatively infant compared to other international RB centers. Throughout these 4 years, there was 1 death among 20 patients with a mortality rate of 5%. The patient had bilateral RB. Her right eye was Group E which has been enucleated, and her left eye was Group D. This child was initially treated with systemic chemotherapy because of progressive disease over the left eye, and enucleation was offered to the parents. However, the parents were adamant about not enucleating the only eye. IAC was commenced with intravitreal chemotherapy as adjunctive therapy. Eventually, this patient succumbed due to pelvis metastasis. Refusal of enucleation is more commonly seen in less-developed countries.[40] Parents were likely to refuse treatment and further management at the point when they were counseled for enucleation in Malaysia.[41,42] Hence, IAC provided an alternative exit route for these patients. Nevertheless, enucleation is inevitable in some eyes and refusal for enucleation could be the contributing factor for metastatic death among these patients.

In terms of intra-arterial chemotherapeutic agents, we initially started with only melphalan infusion

Table 4: Literature reviews of intra-arterial chemotherapy therapy

Study	Year	Country	Number of eyes	Success rate of cannulation (%)	Globe salvage (%)						Complications, % (eye)			Mortality, % (patient)
					Group A-C	Group D	Group E	Primary IAC	Secondary IAC	Overall	Stroke	Periorbital edema	Periorbital pigmentation	
Vajzovic *et al*.[10]	2011	US	12	100	-	75	-	100	73	75	0	8 (1)	0	0
Gobin *et al*.[19]	2011	US	95	99	-	-	-	-	-	80	0	11 (10)	0	0
Munier *et al*.[20]	2011	Switzerland	13	97	-	-	-	-	-	-	0	23 (3)	0	0
Suzuki *et al*.[15]	2011	Japan	408	99	83	45	30	-	-	54	0	0	0	0
Peterson *et al*.[21]	2011	US	17	100	-	77	-	-	77	77	0	0	0	0
Muen *et al*.[22]	2012	UK	15	-	-	-	-	-	-	87	0	20 (3)	0	0
Palioura *et al*.[23]	2012	US	37	-	-	-	-	88	80	86	0	5 (2)	0	0
Venturi *et al*.[24]	2013	Italy	41	92	-	-	-	59	96	80	0	61 (25)	0	0
Thampi *et al*.[25]	2013	US	20	100	100	55	50	58	88	70	0	13 (2)	0	0
Schaiquevich *et al*.[26]	2013	Argentina	8	100	-	-	-	-	75	75	0	25 (2)	0	0
Ghassemi *et al*.[27]	2014	Iran	24	-	-	-	-	-	-	63	0	50 (12)	0	0
Taich *et al*.[28]	2014	Argentina	27	-	-	-	-	100	86	89	0	0	0	0
Shields *et al*.[3]	2014	US	70	99	100	94	36	72	62	67	0	5 (10)	0	0
Ong *et al*.[17]	2015	Taiwan	17	91	75	100	50	67	55	59	0	12 (2)	0	8 (1)
Michaels *et al*.[12]	2016	US	19	100	-	-	-	43	67	58	0	63 (12)	26 (5)	0
Leal-Leal *et al*.[29]	2016	Mexico	14	79	86	50	-	-	-	55	7 (1)	0	0	0
Hahn *et al*.[30]	2016	Korea	13	100	100	60	60	-	-	70	0	23 (3)	0	0
Tuncer *et al*.[31]	2016	Turkey	26	97	-	67	-	67	-	67	0	54 (13)	13 (3)	0
Shields *et al*.[32]	2016	US	66	-	100	83	48	-	-	73	0	0	0	0
Abramson *et al*.[33]	2016	US	112	-	-	-	-	85	74	79	0	22 (25)	0	1 (1)
Abramson *et al*.[16]	2016	US	120	-	100	100	90	-	-	97	0	0	0	0
Chen *et al*.[9]	2017	China	107	99	100	79	62	93	79	79	0	14 (15)	0	0
Munier *et al*.[11]	2017	Switzerland	25	93	-	100	-	100	-	100	0	20 (5)	0	0
Rishi *et al*.[34]	2017	India	10	-	100	83	0	-	-	80	0	0	10 (1)	0
Abramson *et al*.[35]	2017	US	106	-	-	88	91	89	-	89	0	0	0	0
Francis *et al*.[13]	2017	US	40	-	-	-	-	68	100	85	0	0	0	0
Rojanaporn *et al*.[6]	2019	Thailand	27	94	100	75	9	57	50	52	0	0	0	4 (1)
Hua *et al*.[36]	2018	China	84	95	-	42	21	-	-	30	0	14 (12)	0	0
Liu *et al*.[5]	2020	Malaysia	14	72	40	14	100	-	38	38	0	21 (3)	0	0
Oporto *et al*.[37]	2021	Chile	35	99	89-100	63	-	-	-	77	0	0	3 (1)	3 (1)
Shields *et al*.[4]	2021	US	341	-	100	86	55	76	71	74	1 (2)	0	0	0
Kiefer *et al*.[38]	2021	Germany	88	-	-	-	-	-	-	68	0	0	0	1 (1)
Liang *et al*.[39]	2022	China	116	-	-	97	77	-	-	87	0	0	0	0
Present study	2022	Malaysia	22	89	75-100	67	43	40	71	64	2 (1)	9 (4)	4 (2)	5 (1)

"-" indicates not available. IAC=Intra-arterial chemotherapy

back in 2014.[5] After studying more published articles recommending additional topotecan on top of melphalan, we started to infuse melphalan plus topotecan for our IAC patients in 2018.[3] Liu *et al* from Malaysia published his work stating that their globe salvage rate was only 38% in 2018 by using Melphalan alone. Hence, I cited his paper and compared to our current paper. It showed improvement from 38% to 63.6%.[5] Such significant improvement might be contributed by additional topotecan in the IAC regime for RB treatment.

There has been ample discussion of complications of IAC, especially in center with lesser experience like us. In our first few years' experience, IAC is considered a safe procedure with vomiting as the most common side effect (26.1%). Nausea and vomiting could be attributed by general anesthetic medications. Out of 46 successful cannulations, there was 1 incident of stroke (2.2%) involving the right middle cerebral artery. The patient developed left-sided focal seizure, and CT revealed an acute right middle cerebral artery territory infarct. Perhaps due to neural plasticity in pediatric patients, that child recovered with no residual weakness.[43] Stroke is a rare but serious complication that can occur during IAC procedure, with only four reported cases of stroke related to IAC by far including this study.[4] The risk of stroke in IAC ranges between 1% and 7% based on our literature reviews in Table 4.[2-6,8-12,15,17,24]

Other than that, we encountered 1 transient oxygen desaturation (2.2%) during IAC procedure, 4 periorbital edema (8.8%), 3 ptosis (6.5%), and 2 hyperpigmented patch over lid (4.4%). Our patients resolved from these complications spontaneously. Overall, the complication rate was comparable to other international RB centers.[3,4,9] Hopefully, the complication rate will be reduced further with time and experience.

The limitation of this study is the small sample size which was constrained by the limited resources in our developing nation. Future studies with larger sample size from a developing country would be very useful.

Conclusion

Our results indicate that IAC is a safe and effective treatment modality for patients with intraocular RB in our populations and health setting. IAC has provided hopes for advanced RB patients to salvage the globe with preservation of some vision. Furthermore, unilateral RB patients can receive primary IAC therapy without exposing themselves to systemic chemotherapeutic agents and the devastating systemic side effects. Finally, careful patient selection and teamwork collaboration between pediatric ophthalmology, pediatric oncology, and interventional radiology are utmost important to provide the best IAC outcome for our young RB patients.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Conflicts of interest

The authors declare that there are no conflicts of interests of this paper.

References

1. Yamane T, Kaneko A, Mohri M. The technique of ophthalmic arterial infusion therapy for patients with intraocular retinoblastoma. Int J Clin Oncol 2004;9:69-73.
2. Abramson DH, Marr BP, Dunkel IJ, Brodie S, Zabor EC, Driscoll SJ, *et al.* Intra-arterial chemotherapy for retinoblastoma in eyes with vitreous and/or subretinal seeding: 2-year results. Br J Ophthalmol 2012;96:499-502.
3. Shields CL, Manjandavida FP, Lally SE, Pieretti G, Arepalli SA, Caywood EH, *et al.* Intra-arterial chemotherapy for retinoblastoma in 70 eyes: Outcomes based on the international classification of retinoblastoma. Ophthalmology 2014;121:1453-60.
4. Shields CL, Dockery PW, Yaghy A, Duffner ER, Levin HJ, Taylor OS, *et al.* Intra-arterial chemotherapy for retinoblastoma in 341 consecutive eyes (1,292 infusions): Comparative analysis of outcomes based on patient age, race, and sex. J AAPOS 2021;25:150.e1-150.e9.
5. Liu CC, Mohmood A, Hamzah N, Lau JH, Khaliddin N, Rahmat J. Intra-arterial chemotherapy for retinoblastoma: Our first three-and-a-half years' experience in Malaysia. PLoS One 2020;15:e0232249.
6. Rojanaporn D, Chanthanaphak E, Boonyaopas R, Sujirakul T, Hongeng S, Ayudhaya SS. Intra-arterial chemotherapy for retinoblastoma: 8-year experience from a tertiary referral institute in Thailand. Asia Pac J Ophthalmol (Phila) 2019;8:211-7.
7. Ding Y, Lin M, Liu H, Zhang W, Wang L, Li Y. Outcomes of post-cataract surgery endophthalmitis referred to a tertiary Center from local hospitals in the south of China. Infection 2011;39:451-60.
8. Dalvin LA, Kumari M, Essuman VA, Shohelly Shipa S, Ancona-Lezama D, Lucio-Alvarez JA, *et al.* Primary intra-arterial chemotherapy for retinoblastoma in the intravitreal chemotherapy era: Five years of experience. Ocul Oncol Pathol 2019;5:139-46.
9. Chen M, Jiang H, Zhang J, Shen G, Jiang Y, Li H, *et al.* Outcome of intra-arterial chemotherapy for retinoblastoma and its influencing factors: A retrospective study. Acta Ophthalmol 2017;95:613-8.
10. Vajzovic LM, Murray TG, Aziz-Sultan MA, Schefler AC, Wolfe SQ, Hess D, *et al.* Supraselective intra-arterial chemotherapy: Evaluation of treatment-related complications in advanced retinoblastoma. Clin Ophthalmol 2011;5:171-6.
11. Munier FL, Mosimann P, Puccinelli F, Gaillard MC, Stathopoulos C,

Houghton S, *et al.* First-line intra-arterial versus intravenous chemotherapy in unilateral sporadic group D retinoblastoma: Evidence of better visual outcomes, ocular survival and shorter time to success with intra-arterial delivery from retrospective review of 20 years of treatment. Br J Ophthalmol 2017;101:1086-93.
12. Michaels ST, Abruzzo TA, Augsburger JJ, Corrêa ZM, Lane A, Geller JI. Selective ophthalmic artery infusion chemotherapy for advanced intraocular retinoblastoma: CCHMC early experience. J Pediatr Hematol Oncol 2016;38:65-9.
13. Francis JH, Iyer S, Gobin YP, Brodie SE, Abramson DH. Retinoblastoma vitreous seed clouds (Class 3): A comparison of treatment with ophthalmic artery chemosurgery with or without intravitreous and periocular chemotherapy. Ophthalmology 2017;124:1548-55.
14. Menon BS, Alagaratnam J, Juraida E, Mohamed M, Ibrahim H, Naing NN. Late presentation of retinoblastoma in Malaysia. Pediatr Blood Cancer 2009;52:215-7.
15. Suzuki S, Yamane T, Mohri M, Kaneko A. Selective ophthalmic arterial injection therapy for intraocular retinoblastoma: The long-term prognosis. Ophthalmology 2011;118:2081-7.
16. Abramson DH, Marr BP, Francis JH, Dunkel IJ, Fabius AW, Brodie SE, *et al.* Simultaneous Bilateral ophthalmic artery chemosurgery for bilateral retinoblastoma (tandem therapy). PLoS One 2016;11:e0156806.
17. Ong SJ, Chao AN, Wong HF, Liou KL, Kao LY. Selective ophthalmic arterial injection of melphalan for intraocular retinoblastoma: A 4-year review. Jpn J Ophthalmol 2015;59:109-17.
18. Abramson DH, Shields CL, Jabbour P, Teixeira LF, Fonseca JRF, Marques MCP, *et al.* Metastatic deaths in retinoblastoma patients treated with intraarterial chemotherapy (ophthalmic artery chemosurgery) worldwide. Int J Retina Vitreous 2017;3:40.
19. Gobin YP, Dunkel IJ, Marr BP, Brodie SE, Abramson DH. Intra-arterial chemotherapy for the management of retinoblastoma: Four-year experience. Arch Ophthalmol 2011;129:732-7.
20. Munier FL, Beck-Popovic M, Balmer A, Gaillard MC, Bovey E, Binaghi S. Occurrence of sectoral choroidal occlusive vasculopathy and retinal arteriolar embolization after superselective ophthalmic artery chemotherapy for advanced intraocular retinoblastoma. Retina 2011;31:566-73.
21. Peterson EC, Elhammady MS, Quintero-Wolfe S, Murray TG, Aziz-Sultan MA. Selective ophthalmic artery infusion of chemotherapy for advanced intraocular retinoblastoma: Initial experience with 17 tumors. J Neurosurg 2011;114:1603-8.
22. Muen WJ, Kingston JE, Robertson F, Brew S, Sagoo MS, Reddy MA. Efficacy and complications of super-selective intra-ophthalmic artery melphalan for the treatment of refractory retinoblastoma. Ophthalmology 2012;119:611-6.
23. Palioura S, Gobin YP, Brodie SE, Marr BP, Dunkel IJ, Abramson DH. Ophthalmic artery chemosurgery for the management of retinoblastoma in eyes with extensive (>50%) retinal detachment. Pediatr Blood Cancer 2012;59:859-64.
24. Venturi C, Bracco S, Cerase A, Cioni S, Galluzzi P, Gennari P, *et al.* Superselective ophthalmic artery infusion of melphalan for intraocular retinoblastoma: Preliminary results from 140 treatments. Acta Ophthalmol 2013;91:335-42.
25. Thampi S, Hetts SW, Cooke DL, Stewart PJ, Robbins E, Banerjee A, *et al.* Superselective intra-arterial melphalan therapy for newly diagnosed and refractory retinoblastoma: Results from a single institution. Clin Ophthalmol 2013;7:981-9.
26. Schaiquevich P, Ceciliano A, Millan N, Taich P, Villasante F, Fandino AC, *et al.* Intra-arterial chemotherapy is more effective than sequential periocular and intravenous chemotherapy as salvage treatment for relapsed retinoblastoma. Pediatr Blood Cancer 2013;60:766-70.
27. Ghassemi F, Ghanaati H, Karkhaneh R, Boujabadi L, Tabatabaie SZ, Rajabi MT. Outcome of retinoblastoma following limited sessions of intra-arterial chemotherapy in iran. Iran J Radiol 2014;11:e16958.
28. Taich P, Ceciliano A, Buitrago E, Sampor C, Fandino A, Villasante F, *et al.* Clinical pharmacokinetics of intra-arterial melphalan and topotecan combination in patients with retinoblastoma. Ophthalmology 2014;121:889-97.
29. Leal-Leal CA, Asencio-López L, Higuera-Calleja J, Bernal-Moreno M, Bosch-Canto V, Chávez-Pacheco J, *et al.* Globe salvage with intra-arterial topotecan-melphalan chemotherapy in children with a single eye. Rev Invest Clin 2016;68:137-42.
30. Hahn SM, Kim HS, Kim DJ, Lee SC, Lyu CJ, Han JW. Favorable outcome of alternate systemic and intra-arterial chemotherapy for retinoblastoma. Pediatr Hematol Oncol 2016;33:74-82.
31. Tuncer S, Sencer S, Kebudi R, Tanyıldız B, Cebeci Z, Aydın K. Superselective intra-arterial chemotherapy in the primary management of advanced intra-ocular retinoblastoma: First 4-year experience from a single institution in Turkey. Acta Ophthalmol 2016;94:e644-51.
32. Shields CL, Alset AE, Say EA, Caywood E, Jabbour P, Shields JA. Retinoblastoma control with primary intra-arterial chemotherapy: Outcomes before and during the intravitreal chemotherapy era. J Pediatr Ophthalmol Strabismus 2016;53:275-84.
33. Abramson DH, Daniels AB, Marr BP, Francis JH, Brodie SE, Dunkel IJ, *et al.* Intra-arterial chemotherapy (ophthalmic artery chemosurgery) for group D retinoblastoma. PLoS One 2016;11:e0146582.
34. Rishi P, Sharma T, Sharma M, Maitray A, Dhami A, Aggarwal V, *et al.* Intra-arterial chemotherapy for retinoblastoma: Two-year results from tertiary eye-care center in India. Indian J Ophthalmol 2017;65:311-5.
35. Abramson DH, Fabius AW, Francis JH, Marr BP, Dunkel IJ, Brodie SE, *et al.* Ophthalmic artery chemosurgery for eyes with advanced retinoblastoma. Ophthalmic Genet 2017;38:16-21.
36. Hua J, Gang S, Yizhou J, Jing Z. Intra-arterial chemotherapy as second-line treatment for advanced retinoblastoma: A 2-year single-center study in China. J Cancer Res Ther 2018;14:106-10.
37. Oporto JI, Zúñiga P, Ossandón D, Zanolli M, Pérez V, López JP, *et al.* Intra-arterial chemotherapy for retinoblastoma treatment in Chile: Experience and results 2013-2020. Arch Soc Esp Oftalmol (Engl Ed) 2021;96:288-92.
38. Kiefer T, Schlüter S, Bechrakis NE, Bornfeld N, Göricke S, Ketteler P, *et al.* Intraarterial chemotherapy for retinoblastoma – Initial experiences of a German reference centre. Klin Monbl Augenheilkd 2021;238:788-96.
39. Liang T, Zhang X, Li J, Hua X, Zhao P, Ji X. Intra-arterial chemotherapy as primary treatment for advanced unilateral retinoblastoma in China. Front Med (Lausanne) 2022;9:855661.
40. Canturk S, Qaddoumi I, Khetan V, Ma Z, Furmanchuk A, Antoneli CB, *et al.* Survival of retinoblastoma in less-developed countries impact of socioeconomic and health-related indicators. Br J Ophthalmol 2010;94:1432-6.
41. Jamalia R, Sunder R, Alagaratnam J, Goh PP. Retinoblastoma Registry report--Hospital Kuala Lumpur experience. Med J Malaysia 2010;65 Suppl A:128-30.
42. Subramaniam S, Rahmat J, Rahman NA, Ramasamy S, Bhoo-Pathy N, Pin GP, *et al.* Presentation of retinoblastoma patients in Malaysia. Asian Pac J Cancer Prev 2014;15:7863-7.
43. Malone LA, Felling RJ. Pediatric stroke: Unique implications of the immature brain on injury and recovery. Pediatr Neurol 2020;102:3-9.