Original Article

Five-Year Experience in Treatment of Retinoblastoma with Intra-Arterial Chemotherapy: A Single-Center Analysis

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Abstract

Purpose: To report our 5-year experience in treating retinoblastoma (RB) with intra-arterial chemotherapy (IAC) as a primary or secondary therapy, without adjuvant intravitreal chemotherapy.

Methods: A retrospective study was conducted on 70 eyes with intraocular RB that were treated with primary or secondary IAC from December 2010-2015. Demographic characteristics, clinical features, tumor control, and treatment complications were compared and reported.

Results: Thirty-seven eyes had received IAC as a secondary therapy after failed/incomplete response to systemic chemotherapy, and 33 eyes had received IAC as a primary treatment. The mean age of patients was 25 ± 8.9 months, and the patients were followed for a mean of 24.5 ± 16.26 months. Overall, enucleation rates were significantly higher in advanced tumors (Group D and E) in both groups (both $P < 0.05$). The main reason for enucleation in this study group was being unresponsive to treatment (27.4%), with 76% of latter patients having vitreous seeds at the time of enucleation. Enucleation rates did not differ significantly between patients receiving primary (18/33, 54%) or secondary IAC (18/37, 48%) ($P = 0.06$). In addition, recurrence and complication rates did not differ significantly between eyes receiving IAC as their primary or secondary treatment ($P > 0.05$).

Conclusion: In primary and secondary treatment of RB with IAC, the main findings that are globe salvage, recurrence, and complication rates were comparable when no adjuvant intravitreal chemotherapy was used.

Keywords: Intra-arterial chemotherapy, Retinoblastoma, Systemic chemotherapy

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Introduction

Retinoblastoma (RB) is the most common primary intraocular malignancy in children.[1-3] With recent advances in treatment, new frontiers such as globe salvage and vision conservation have emerged.

Multiple treatment options have been introduced to RB, treatments providing a possibility for globe salvage include systemic chemotherapy and intra-arterial chemotherapy (IAC) with and without adjuvant therapies, i.e., cryotherapy, laser photocoagulation, transpupillary thermotherapy (TTT), and/or brachytherapy.[3-6] In advanced cases, intravitreal chemotherapy and periocular chemotherapy have also been used as an adjuvant.[5-7]

Systemic chemotherapy combined with local consolidation in intraocular RB treatment has shown favorable success rates,[7,8] including 30%–70% chance of globe salvage,[8-11] as well as prevention of metastasis and secondary cancers.[7] However, systemic chemotherapy could be ineffective in advanced RB control (Groups D and E) due to a higher likelihood

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of local recurrences, requiring IAC or enucleation.[7,12,13] IAC is distinctively beneficial in local delivery of higher dose chemotherapy agents and minimizing side effects of systemic chemotherapy.[4] Successful uses of IAC in treating unilateral and also advanced tumors have been reported with promising results on globe salvage (approximately 30%–100%, depending on the tumor group).[4,8,14-16] It has also been successfully used in the treatment of recurrent or irresponsive tumors after chemotherapy, alleviating the need for enucleation.[14] Nonetheless, some concerns still remain with IAC including its limitations in controlling the systemic spread of the disease and related ocular complications, mostly due to vascular compromise in ophthalmic artery, retinal artery, or choroidal vessels.[7] In addition, it is shown that IAC is less effective in treating Group E tumors and those with vitreous seeds.[4]

To shed further light on IAC and its shortcomings, an expansive study was conducted to investigate IAC outcomes. In some cases, IAC was the sole treatment method, whereas in others, it was the primary or secondary element of a hybrid treatment. The primary aim of the study was to provide further comparative evidence on the efficacy of IAC as a primary or secondary treatment in controlling RB, before the availability of intravitreal chemotherapy in the center where this study was conducted, over a period of 5 years.

Methods

The retrospective chart review was performed and included 62 consecutive patients with RB (unilateral or bilateral) treated with IAC at the ocular oncology department of Farabi Eye Hospital from 2010 to 2015. The study was approved by the ethics committee of Tehran University of Medical Sciences and it adhered to the tenets of the Declaration of Helsinki. The patient has provided consent for use of the photos.

All patients receiving IAC either as a primary or secondary treatment were included. Exclusion criteria were short (<3 months) follow-up time, those who could not be followed in our center, and those who received any type of intravitreal chemotherapy. The data provided in this study are a subsection of an ongoing cohort study in Farabi Eye Hospital.[5,6,17] The reported data are for pre-intravitreal chemotherapy episodes in our center to isolate the effect of IAC on the treatment of RB. The impact of concomitant use of IAC and intravitreal chemotherapy was not in the scope of this study.

Initially, all patients were examined under general anesthesia by one or two ocular oncologists (F.G., A.K.). Examinations included indirect ophthalmoscopy, RetCam imaging (Massey Industries, Dublin, CA, USA), and B-scan if needed. Findings of detailed examinations were documented in large fundus drawings and preprepared charts. All cases were graded based on the International Classification of RB (ICRB).[13] In addition, brain and orbital magnetic resonance imaging (MRI) was also performed on all patients to assess intracranial/intraorbital extension, or associated tumors, when necessary.

Based on the examining ophthalmologist's decision, patients with unilateral RB were considered for primary IAC treatment. Few patients, with unilateral RB, received systemic chemotherapy instead of IAC for their initial treatment, based on their parents' desire or unsuccessful cannulations of ophthalmic artery. Patients with previous systemic chemotherapy and incomplete response or recurrence were considered for secondary IAC treatment. All patients with bilateral RB received systemic chemotherapy as the first line of therapy. In patients needing bilateral IAC (bilateral cases that showed recurrence or were unresponsive to primary systemic chemotherapy), the procedure was done in two different sessions.

Patients were referred to intervention radiologists for IAC. The chemotherapy protocol consisted of 5 mg melphalan and 0.6–1 mg topotecan, based on the patient's age, with or without 25 mg carboplatin each adjusted to 10–30 ml saline. Systemic chemotherapy regimens included vincristine, etoposide, and carboplatin (VEC) as usual or, if indicated, vincristine, prednisolone, etoposide and chlorambucil (OPEC) protocol. Adjuvant TTT and cryotherapy were done in follow-up visits if needed. Patient follow-up was done every month after IAC until complete tumor and vitreous/subretinal seeding regression.

Recorded data were as follows: demographic data, hereditary pattern, laterality, presenting symptoms, time from symptoms to diagnosis, intraocular pressure, tumor characteristics/staging (based on ICRB) and presence of seeds and subretinal fluid in the first examination, the first treatment protocol after EUA, details of treatments prior and subsequent to IAC (chemotherapy/TTT/cryotherapy, number of treatment sessions), IAC type (double or triple agent), number of IAC sessions, IAC complications, regression type in response to IAC[18] (3 and 6 months after IAC), recurrence (time, type, location relative to the presenting tumor, and treatment response), enucleation after IAC, time from IAC to enucleation, cause of enucleation, pathologic findings, follow-up time, and metastasis.

The primary outcome measures were globe salvage and enucleation rates in patients treated with primary or secondary IAC. The secondary outcome measures were recurrence rates, IAC complications, and the contributing factors.

Statistical analyses were performed with SPSS software (version 25) (SSPS Inc., Chicago, IL, USA). The normality of data was examined by Shapiro–Wilk test. The Chi-square test and Fisher's exact test were performed to compare categorical data. Continuous data were compared using Mann–Whitney *U*-test. All reported *P* values were two-tailed. $P < 0.05$ was considered to be statistically significant. Time to enucleation (globe salvage) and time to recurrence were analyzed using Kaplan–Meier method.

Results

The study included 70 eyes of 62 consecutive, IAC-treated RB patients in a 5-year period. The mean follow-up time was 24.5 ± 16.26 months (median 21.5, range 3–95). Three eyes had less than 6 months (3 and 5 months) follow-up time, and 53 eyes (75%) were followed over a year. Patients demographic data are listed in Table 1. The geographic positioning of provinces, where the patients came from, did not show any significant relevance to RB occurrence rate [Table 1]. At presentation, 41 patients (66.13%, 41 eyes) had unilateral, and 21 patients (33.87%, 29 eyes) had bilateral involvement. Table 2 captures details of baseline tumor characteristics. Fifty-five (78.5%) eyes were classified as either Group D (n = 39, 53%) or Group E (n = 16, 23%). The remaining eyes had less advanced disease. Vitreous seed (s) were noted in 46 (65.7%) eyes and subretinal fluid in 45 (64.3%) eyes. At presentation, none of the patients in this study had vitreous hemorrhage, three patients had cataract, three patients had anterior chamber seeds, and one patient had iris neovascularization. Baseline concurrent ocular signs are listed in Table 2.

Among 70 eyes enrolled in this study, IAC had been the primary treatment in 33 (47%) and the secondary treatment in 37 (53%) eyes. Five patients had failed cannulation of ophthalmic artery either through internal carotid or external carotid artery and were not included. All patients had received the three chemotherapeutic agent IAC infusion (melphalan, topotecan, and carboplatin). Five patients received bilateral IAC. Of 37 eyes treated secondarily with IAC, all had received systemic chemotherapy (VEC/OPEC) as the initial treatment. In patients who had received IAC as their initial treatment (n = 33), 13 received no additional systemic chemotherapy, and 20 patients received systemic chemotherapy as a rescue treatment because of unresponsiveness or partial response (OPEC [n = 1] and VEC [n = 19]). Additional information about the adjuvant treatments used, such as TTT and cryotherapy, is captured in Table 3. Patients had mostly shown type 3 of regression (partially calcified mass) in response to IAC and systemic chemotherapy at months 3 and 6 after treatment [Figure 1]. The overall management details are provided in Table 3.

Fifty-seven percent (40/70) of eyes had experienced recurrence at some point during their course of treatment. Sixteen out of 33 patients treated primarily with IAC and 24/37 patients treated primarily with systemic chemotherapy had experienced recurrence during their treatment since initial diagnosis [P = 0.08, Table 3]. Eyes that had received systemic chemotherapy as their initial treatment had undergone an average number of 6.3 ± 3.3 sessions (range, 1–14) of systemic chemotherapy before the first recurrence. The mean time from IAC to recurrence was 6.3 ± 4.7 months (range, 2–16.5). In 8/16 (50%) patients in the primary IAC group and 16/24 (66.6%) patients in the secondary IAC group, the recurrence responded to treatment. Overall, the most common type of recurrence was the appearance of new tumors (80%), followed by vitreous seeds (20%). In 42% of patients,

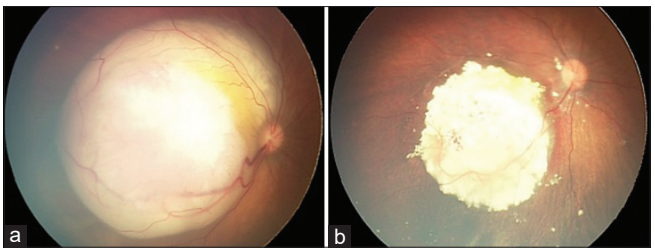

Figure 1: As a success story, a 24-month-old baby with Group C posterior pole retinoblastoma treated with three sessions of intra-arterial chemotherapy (a and b, before and after treatment, respectively)

Table 1: The demographics of the patients with retinoblastoma tumor treated with intra-arterial chemotherapy without intravitreal chemotherapy

	All eyes (n=70)	Eyes treated with IAC as primary therapy (n=33)	Eyes treated with IAC after partial response or relapse with other therapies (n=37)	*P*
Age in months; mean±SD, median (range)	25.4±8.9, 24 (6-84)	28.3±1.7, 24 (6-84)	22.9±12, 14 (6-66)	0.23
Sex, *n* (%)				
Female	33 (47)	13 (39.4)	20 (54)	0.28
Male	37 (53)	20 (60.6)	17 (46)	
Study eye, *n* (%)				
Right	36 (51)	18 (54)	18 (48)	0.96
Left	34 (49)	15 (4)	19 (52)	
Symptoms duration until diagnosis in months; mean±SD (range)	1.3±1.4 (0-6)	1.2±1.2 (0-4)	1.6±1.8 (0-6)	0.71
Positive family history for RB, *n* (%)	6 (8.6)	2 (6.0)	4 (10.8)	0.42
Region of origin in Iran, *n* (%)				
North	10 (14.2)	5 (15.1)	5 (13.5)	0.57
East	7 (10)	4 (12.1)	3 (8.1)	
West	12 (17.1)	8 (24.2)	3 (8.1)	
South	1 (1.4)	0	1 (2.7)	
Central	40 (57.1)	15 (45.4)	25 (67.5)	

RB: Retinoblastoma, IAC: Intra-arterial chemotherapy, SD: Standard deviation

Table 2: General characteristics of the tumors at the time of diagnosis

	All eyes (*n*=70)	Eyes treated with IAC as primary therapy (*n*=33)	Eyes treated with IAC after partial response or relapse with other therapies (*n*=37)	*P*
ICRB classification, *n* (%)				
Group A	3 (4.2)	2 (6)	1 (3)	0.07
Group B	3 (4.2)	0 (0)	3 (8)	
Group C	9 (12.8)	2 (6)	7 (19)	
Group D	39 (52.8)	18 (55)	21 (57)	
Group E	16 (22.8)	11 (33)	5 (13)	
Number of tumors per eye; mean±SD, median (range)	1.9±2.1, 1 (1-12)	1.7±1.9, 1 (1-10)	2.1±2.2, 1 (1-12)	0.4
Largest diameter (mm); mean±SD, median (range)	14±6.3, 15 (0.1-30)	14.8±6.5, 16 (0.1-30)	13.3±6.1, 15 (7-30)	0.3
Thickness (mm) mean±SD, median (range)	8.1±3.1, 8 (2.5-13)	8.1±3.7, 9 (3-13)	8.2±3.1, 8 (2.5-13)	0.9
Distance to optic nerve (mm); mean±SD, median (range)	1.4±3.1, 0 (0-18)	0.9±1.9, 0 (0-8)	1.8±3.9, 0 (0-18)	0.2
Distance to foveola (mm); mean±SD, median (range)	1.4±3.3, 0 (0-18)	0.9±2.3, 0 (0-10)	1.89±3.9, 0 (0-18)	0.2
Quadrant of involvement, *n* (%)				
1 quadrant	46 (65.7)	22 (66.6)	24 (64.8)	0.5
2 quadrants	10 (14.2)	4 (12.1)	6 (16.2)	
3 quadrants	5 (7.1)	1 (3)	4 (10.8)	
4 quadrants	3 (4.2)	2 (6)	1 (2.7)	
No view	6 (8.5)	4 (12.1)	2 (5.4)	
Subretinal fluid, *n* (%)	45 (64.3)	24 (73)	21 (57)	0.12
Vitreous seed, *n* (%)	46 (65.7)	25 (73)	21 (57)	0.07
Feeder vessel, *n* (%)	36 (51)	15 (45.5)	21 (56.8)	0.40

ICRB: International Classification of Retinoblastoma, IAC: Intra-arterial chemotherapy, SD: Standard deviation

Table 3: Treatment features and outcomes

	All eyes (*n*=70)	Eyes treated with IAC as primary therapy (*n*=33)	Eyes treated with IAC after partial response or relapse with other therapies (*n*=37)	*P*
Number of systemic chemotherapy infusions; mean±SD, median (range)	6.5±5.7, 6 (0-27)	5.0±5.9, 4 (0-27)	8.1±5.2, 6 (1-24)	**0.04**
Additional therapy used, *n* (%)				
TTT	45 (64.2)	17 (51.5)	28 (75.6)	0.1
Cryotherapy	27 (38.5)	5 (15.1)	22 (59.4)	**0.00001**
Systemic chemotherapy	57 (81.4)	20 (60.6)	37 (100)	-
Plaque radiotherapy	0	0	0	-
Response to treatment, *n* (%)				
Complete or partially responsive	49 (70)	22 (66.7)	27 (72.9)	0.45
None responder	21 (30)	11 (33.3)	10 (27.0)	
Recurrence during the course of disease, *n* (%)	40 (57.1)	16 (48)	24 (35.1)	1.00
Recurrence time after diagnosis (month); mean±SD	7.7±6.0	6.3±4.8	8.1±6.4	0.51

P values in boldface are statistically significant. *IAC. TTT: Transpupillary thermotherapy, IAC: Intra-arterial chemotherapy, SD: Standard deviation

recurred tumors were more than five. The recurred tumor had appeared both near (47%) and far from the past tumor (42%), almost equally. The location of the tumor was 41.2% in the equator, 29.4% in the periphery, 17.6% in both the equator and periphery, and 11.8% in the equator and posterior pole.

Sixty-six percent (34/54) of eyes showed complications in relation to IAC treatment. Eleven eyes (17.6%) led to severe visual impairment (severe pigmentary changes and central retinal artery occlusion), and 3 eyes (4.8%) became phthisic eventually [Table 4]. Differences between the two groups were not significant ($P > 0.05$).

Thirty-six (51.4%) eyes were eventually enucleated. The mean globe survival time from the initiation of treatment was 21.2 ± 17 months (median 18.5, range 5–73). The mean globe survival time from the start of IAC was 11.7 ± 13 months (median 9, range 1–61). Enucleation rate did not differ significantly between patients receiving primary (18/33, 54.5%) or secondary IAC (18/37, 48.6%) ($P = 0.06$). In eyes which were eventually enucleated, 18 (50%) had received primary systemic chemotherapy, 10 (27.8%) had received secondary systemic chemotherapy, and 8 (22.2%) had not received systemic chemotherapy ($P > 0.01$).

Table 4: Ophthalmic complications

	All eyes (n=70), n (%)	Eyes treated with IAC as primary therapy (n=33), n (%)	Eyes treated with IAC after partial response or relapse with other therapies (n=37), n (%)	P
Without complications	33 (47.1)	14 (42.4)	19 (51.4)	0.48
With complications	37 (52.9)	19 (57.5)	18 (48.6)	
Difference between the two groups of primary and secondary IAC in complication types				
Vitreous hemorrhage	13 (18.6)	5 (15.2)	8 (21.6)	0.42
Preretinal hemorrhage	3 (4.3)	1 (3.0)	2 (5.4)	
Phthisis	3 (4.3)	3 (9.1)	0 (0.0)	
Cataract	5 (7.1)	4 (12.1)	1 (2.7)	
Arterial occlusion	4 (5.7)	1 (3.0)	3 (8.1)	
Severe pigmentary changes	6 (8.6)	3 (9.1)	3 (8.1)	
Hypotonia	-	-	-	
Hyphema	1 (1.4)	1 (3.0)	0	
Combination (vitreous hemorrhage + CRAO + cyclitic membrane + phthisis)	1 (1.4)	1 (3.0)	0	
Falciform fold	1 (1.4)	0	1.0 (2.7)	

IAC: Intra-arterial chemotherapy, CRAO: Central retinal artery occlusion

Enucleation rates were significantly higher in advanced tumors (Groups D and E), in eyes receiving IAC (P = 0.001) or systemic chemotherapy (P = 0.04) as their primary treatment. Furthermore, enucleation rates were significantly higher in tumors with larger mean diameters (15.7 ± 5.9 mm compared to 12.3 ± 6.2 mm, P = 0.02). The rate of enucleation was not significantly related to other initial tumor characteristics listed in Table 2. In eyes receiving IAC as their primary treatment, 0/2 (0%) of Group A, 0/2 (0%) of Group C, 7/18 (38.9%) of Group D, and 11/11 (100%) of Group E eyes were eventually enucleated. Of 18 Group D eyes, 2/3 of bilateral eyes (66.7%) and 5/15 of unilateral eyes (33.3%) were enucleated. In eyes receiving IAC as their secondary treatment, 0/1 (0%) of Group A, 0/3 (0%) of Group B, 4/7 (57.1%) of Group C, 9/21 (42.9%) of Group D, and 5/5 (100%) of Group E eyes were eventually enucleated.

The main reason for enucleation in this study group (n = 28 with documented cause) was unresponsiveness to treatment (n = 17, 27.4%) followed by appearance of new tumor (n = 4, 6.5%), neovascular glaucoma (n = 3, 4.8%), neovascularization of the iris (n = 2, 3.2%), and vitreous hemorrhage and phthisis (both n = 1, 1.6%). Seventy-six percent (13/17) of patients unresponsive to therapy, including 6 of no response and 7 of incomplete response cases, had vitreous seeds at the time of enucleation. Pathologic data on enucleated eyes (n = 20) showed that the majority of enucleated eyes had poorly differentiated RB (n = 16, 80%) followed by one with partially differentiated (n = 3, 15%) and another one with well-differentiated RB (n = 1, 5%). The rate of enucleation did not differ significantly between eyes with or without IAC complications but differed significantly between different types of complications (P > 0.05). All eyes with hyphema, hypotony, and falciform retinal folds and 91.7% of cases with vitreous hemorrhage were eventually enucleated.

Discussion

In this study, enucleation rates did not differ significantly between patients who had received IAC as their primary or secondary treatment. However, enucleation rates were significantly higher in advanced tumors in both treatment groups.

Tumor characteristics of RB patients in this study were mostly similar to those reported by prior studies in tertiary centers.[8,19-21] Survival rates for eyes treated with IAC after recurrence/incomplete response with primary systemic chemotherapy were marginally lower in this study (51.4%) relative to those in prior studies. For instance, Shields *et al*. reported 62% globe salvage for secondary treated eyes[8] and Gobin *et al*. reported 58.4% globe salvage for eyes that failed to respond to systemic chemotherapy prior to IAC.[16] Both studies had mostly included advanced tumors, similar to those in this study. In another study, specifically on advanced tumors (Groups D and E), the globe survival after IAC for unresponsive cases to systemic chemotherapy was reported to be 57%[22] a fairly comparable rate to that reported in this study. Higher number of advanced groups of the disease at the time of diagnosis, the quality of the used drugs, or some unknown technical issues at the time of IAC could be the cause for this discrepancy. The use of IAC, as a rescue treatment for unresponsive tumors to prior systemic and/or local therapies, improved the likelihood of globe salvage but not as much as globe salvage rates reported on eyes with IAC as the primary, rather than a rescue treatment.[19,23,24] It can be concluded that the main interference factor in the globe survival is the recurrence and occurrence of an unresponsive type of tumor to any present treatment[25] rather than the type of treatment.

Combination of systemic chemotherapy and IAC, a known treatment for advanced tumors, was needed for 60% of eyes

receiving IAC as their primary treatment in this study. The use of IAC did not eliminate the need for systemic chemotherapy, but the number of infusions was significantly reduced in patients treated primarily with IAC. Moreover, 50% of the eyes in the latter group, receiving combination therapy, were saved from enucleation.

In eyes treated primarily with IAC, the globe survival rate was 100% for less advanced A to C tumors, similar to prior studies.[8,19] For more advanced tumors, the survival rate was between 66% and 100% and relatively less compared to prior studies.[8,19,24,26,27] Munier *et al*.[27] used extensive focal therapy, including cryotherapy, thermotherapy, and photocoagulation, in 20 (out of 25) patients early in the treatment course. From five reported recurrences, all were responsive to salvage therapy including redeployment of extensive focal therapy and intravitreal melphalan for persistent or recurrent vitreous disease.[27] In this study, intravitreal seeding was treated after complete treatment of main tumors and cases receiving intravitreal chemotherapy were excluded from the study to isolate the effect of IAC on globe survival. Thermotherapy and cryotherapy were used as adjunctive treatments in both groups if needed. As reported previously, a limitation of IAC is that it could not always control vitreous seeding,[28] as also seen in this study.[4] The main reason for enucleation in this study was unresponsiveness of the main tumor to treatment and 76% of those unresponsive cases were patients with vitreous seeds. In prior studies, the intravitreal chemotherapy, as an adjuvant to control recurrent/persistent vitreous seeds, had shown very promising results in controlling the seeding and had led to avoidance of enucleation.[4,26,29] In light of the preceding, the difference in treatment protocol, including the use of intravitreal melphalan, might have led to better results reported by Munier *et al*.[27]

Recurrences are hard to control and could lead to unfavorable prognosis and eventual enucleation.[4,8,19,20] In this study, the mean time from IAC to recurrence was approximately 6 months, consistent with prior studies.[20] Tuncer *et al*. reported that most recurrences occurred between the month 6th and 15th of IAC treatment and globe survival became stable after at least 2 years.[20] Prior studies, with higher globe salvage rates, had a shorter mean follow-up time of about 16 months, in most of their cases, compared to this study.[8,19,24] Tuncer *et al*. reported a similar globe survival rate of 66% for Group D tumors, treated primarily with IAC and with a mean follow-up time of 29 months.[20] Munier *et al*.[27] and Tuncer *et al*.[20] reported 24% (6/25) and 29% (7/24) recurrences, respectively. Both studies looked into unilateral Group D RB and primary IAC (single-agent melphalan) with 24 months of follow-up, at the least. Recurrence rates were higher in our study, with the mean follow-up time of 24 months. Those higher rates could be due to a larger sample size in this study as well as differences in the used chemotherapy agents in primary IAC.

Fifty percent of recurrences in the primary IAC group and 66.6% of recurrences in the primary systemic chemotherapy group were unresponsive to treatment. That, also, might have contributed to higher enucleation rates observed in this study. Most recurrences were as new tumors in this study. Observations made in this study suggest that the equator and peripheral retina should be examined more carefully in patients with responsive RB, as recurrences tend to occur more frequently in these regions. Prior studies also showed that Group E tumors were less responsive to IAC and more prone to recurrences.[2] In this study, 33% of eyes in the primary IAC group were group E and were all enucleated eventually, another likely reason for relatively higher enucleation rates in this study.

The most prevalent form of complication was vitreous hemorrhage, consistent with findings of prior studies using IAC for RB.[22,27] The incidence of vitreous hemorrhage was higher in this study and the incidence and type of other complications were relatively similar to those of prior studies using IAC for RB.[22,27] In previous studies, complications appeared to be related to the type of used chemotherapy agent,[2] the dose,[29,30] and the utilized technique.[2] Given that, the relatively higher incidence of vitreous hemorrhage in this study could be due to the use of three agents and its likely impact on rapid regression. It could also be related to the utilized agent delivery technique.[30] Dalvin *et al*.[31] showed experience in performing this highly specialized procedure is an important factor in predicting IAC-related complications such as vascular events due to the long learning curve associated with this procedure for the interventionists. In light of that, the higher rate of complications seen in this study could have been due to insufficient experience of interventionists at the university hospital in the early phase of the study period. Vitreous hemorrhage, hyphema, hypotonia, and falciform folds were predictors and biomarkers for enucleation.

It is noteworthy to mention that this study had limitations including its retrospective nature, relatively small cohort size, and relatively short follow-up time. A longer follow-up time could potentially address the long-term stability of observations.

In this retrospective study of patients treated with IAC as the primary or rescue (secondary) treatment of advanced intraocular RB who had not undergone intravitreal chemotherapy, the rates of globe salvage, recurrence, and complications were comparable. In comparison to previous studies, the global salvage rate was somewhat lower, but the rates of recurrence and complications were significantly greater.

In conclusion, this research reveals that in the cohort of patients included in this retrospective study, IAC was not an effective therapy on its own in advanced RB (Grade E). Sight-threatening complications, such as vitreous hemorrhage, hyphema, hypotony, and falciform retinal folds, were predictors of subsequent enucleation.

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Conflicts of interest

There are no conflicts of interest.

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