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The Role of Intra-Arterial Chemotherapy in the Manegment of Advanced Retinoblastoma; Group D & E

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Abstract

Background: The treatment modalities for managing retinoblastoma have evolved in the past decade. While globe-salvage still relies heavily on intravenous chemotherapy, tumors in advanced stages D and E that failed chemotherapy are now referred for intra-arterial chemotherapy (IAC) to avoid enucleation.

Aim of the Study: To evaluate the effectiveness and complications of intra-arterial chemotherapy (IAC) for treating advanced refractory group D and E retinoblastoma (RB).

Material and Methods: 30 intro-ocular advanced refractory retinoblastoma of 26 consecutive patients who received IAC were included in the study during the period between November 2013 and January 2017. These patients failed to respond adequately to a standard systemic chemotherapy (i.e., carboplatin, vincristine, and etoposide) with or without local therapy. Clinical outcomes and complications of these patients were reviewed.

Results: All our patients received IAC with injection of melphalan. The mean follow-up period was 14.2 months after final IAC (ranged from 6 to 20 months). The rate of overall globe salvage was 95% in Group D and 30% in Group E of this study. Short-term ocular adverse events included eyelid edema (n=15, 50%), bulbar conjunctiva congestion (n=7, 23.3%), mild ptosis (n=5, 16.7%) and long-term complications included ophthalmic artery spasm with reperfusion (n=2, 6.7%) retinal atrophy (n=1, 3.3%). Fever was observed after IAC in 10 patients and transient vomiting was observed in 16 patients.

Conclusion: IAC can be an evolving optional treatment to save Group D RB that failed in systemic chemotherapy and were destined for enucleation. However, it should be cautioned for Group E. Both the ocular and systemic toxicities of IAC were within tolerance.

Key Words: *Intra-arterial chemotherapy – Advanced retinoblastoma – Melphalan.*

Introduction

RETINOBLASTOMA (RB) is the most common intraocular tumor in pediatric age group. Management of subretinal seeds (SRS) or vitreous seeds (VS) in RB poses a therapeutic challenge with poor response to conventional systemic chemotherapy, often necessitating enucleation. Intra-arterial chemotherapy (IAC) was first introduced by Reese et al., in 1958 [1], which involved direct delivery of chemotherapeutic agent into the carotid artery. In its current form, as established by Abramson et al., [2] IAC involves selective ophthalmic artery catheterization (OAC) under fluoroscopic guidance for targeted chemotherapeutic drug delivery to the affected eye.

OAC allows many RB cases, which previously were scheduled for enucleation, to be saved, including some of group E eyes. Since the previous standard of care, systemic chemotherapy, had relatively poor success at saving group D eyes, we wanted to assess our success rates in treating these eyes using our OAC technique. In addition, intravenous chemotherapy is associated with many systemic side effects, including neutropenia during treatment and possibly secondary acute myelogenous leukemia (AML) years later [3].

However, complications related to OAC have likewise been reported by various authors that elicited that all adverse ocular events could be resolved spontaneously and systemic toxicities of IAC mostly are within tolerance [4]. In this study we report our success rates with OAC for group D and E retinoblastoma both as primary treatment (in one patient), as well as for patients who had previously failed other forms of treatment (25 patients) as secondary adjuvant treatment to avoid enucleation.

Patients and Methods

The current work was a prospective analysis approved by the Faculty of Medicine Ethics Committee of the Cairo University; cases were supplied

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by the Kasr El Ainy and Sheikh Zayed medical Hospitals and have given informed consent for their used data. The study included 26 patients with 30 intra ocular retinoblastoma, 12 female (46%) and 14 males (54%) with age range at first presentation 5-24 months. Patients were classified according to the original International Classification for Intraocular Retinoblastoma.

Inclusion criteria:

For intra-arterial chemotherapy (IAC) were Group D and E retinoblastoma with the presence of viable unilateral or bilateral retinoblastoma in patients aged 4 months or older either newly diagnosed or with partial remission/or relapse after focal therapies including cryotherapy, laser ablation, brachytherapy, and external beam radiotherapy, or the association of them, and/or systemic chemotherapy.

Exclusion criteria:

- Patients were excluded if the RB could adequately respond to a standard systemic chemotherapy or could be controlled with focal treatments alone as laser, cryotherapy, or brachytherapy (Group A,B and C RB).
- Metastatic RB with extra ocular disease extent, intracranial metastatic disease.
- Patients younger than 4 months and those with abnormal renal or hepatic function, congenital cerebral anomalies, coagulopathy or cardiomyopathy.

Methodology in details:

Our technique of IAC was the slandered technique described worldwide [5]. All IAC procedures were performed while the patients were under general anesthesia. A 4-French (4-F) vascular sheath was placed into the femoral artery using the Seldinger technique. Heparin (75 IU/kg) was administered via intravenous injection to avoid thrombosis. A 4-F Cobra guide catheter (Terumo, Japan) was guided into the internal carotid artery on the side of the affected eye. An arteriogram was performed to visualize the ocular and cerebral vasculature. Anteroposterior and lateral views of the intracranial circulation were obtained to select the best view to show the take off of the ophthalmic artery from the internal carotid.

Under the fluoroscopy and roadmap guidance, we selectively catheterized the ophthalmic artery with a 1.5-F microcatheter (Marathon Flow directed microcatheter, Covidien, Irvine, CA, USA). As soon as the microcatheter was in a stable position at the ostium of the ophthalmic artery, a selective ophthalmic artery angiogram was obtained. The chemotherapeutic agents in the standard protocol included melphalan±topotecan/carboplatin but used melphalan only in our study. The chemotherapy drug were diluted with saline to obtain a volume of 20-30cm^3, which were administered in a pulsatile fashion over 30min with a rate of 1ml/min to avoid streaming and inhomogeneous drug delivery.

The dose of chemotherapeutic agent was selected according to the response from the previous procedure of IAC. When the infusion was completed, the microcatheter was withdrawn and the sheath was removed. Hemostasis was then performed by manual compression for 10-15min. Interventional radiologists performed each IAC. The technical success rate of IAC (i.e., successful injection of melphalan into the ophthalmic artery) was recorded.

In case of selection of the ophthalmic artery was not feasible other alternative techniques were used. One alternative technique used was through the ipsilateral middle meningeal artery anastomosis to the orbit. Where the middle meningeal artery was catheterized and performed selective angiography to determine whether the orbital branch was well developed. If it was, then selective catheterization of this orbital branch permitted the injection of chemotherapy selectively into the orbital vasculature. If it was not well developed, then we either discontinued the procedure or elected to use the "Japanese technique," which consists of placement of a temporary balloon to occlude the internal carotid artery above the origin of the ophthalmic artery and infusion into the internal carotid artery below the balloon. A second Omnipaque angiography confirmed microcatheter flow towards the ocular globe and minimal or absence of backflow to the internal carotid artery.

The child was monitored for 6 hours before discharge. A sterile dressing over the cannulation wound in the leg was maintained for 2 days. Oral aspirin (40mg) was advised for 2 weeks, and topical ophthalmic application of antibiotic-steroid ointment and cycloplegic eye drops was recommended for 2 weeks. Blood counts were performed prior to IAM and 1 and 10 days after each treatment.

All patients received the first IAM treatment as soon as possible after diagnosis and approval by the Retinoblastoma team. Second and third doses were infused on days 21 and 42. A detailed evaluation of response and ocular integrity was performed 2 weeks after each treatment.

Our standard therapy included a cycle of about three infusions of IAM at an interval of 3 to 4 weeks followed by focal therapy. However, additional cycles were allowed in eyes showing at least partial response but still not amenable for focal therapy. In case of complete regression was documented with no sign of tumor or seed viability, then further IAC was not performed. On the other hand, tumors with increased size or maintained tumor vascularity after two IAC treatments were deemed as IAC failures, and the eyes were enucleated. If the eyes involved in this study experienced a recurrence again after IAC treatment and the tumor of relapse could not be controlled with focal treatments alone (laser, cryotherapy or brachytherapy), the eyes were also enucleated.

At each 4-week follow-up, detailed ophthalmic examination was performed by the treating ocular oncologist including external examination, visual acuity testing, intraocular pressure measurement, pupil and motility evaluation, and a complete fundus examination with the patient under anesthesia, including RETCAM III digital photography, B-scan sonography (10MHz) and ERG testing. During follow-up, Each tumor was analyzed for size in greatest basal dimension (millimeters) and thickness (millimeters) using indirect ophthalmoscopy and ultrasonography, distance to the optic nerve and foveola (millimeters), associated vitreous seeds (present, absent), extent of vitreous seeds, associated subretinal fluid (present, absent), percentage of retinal detachment (0%- 100%), and subretinal tumor seeds (present, absent) and their location. Per protocol, adjunctive thermotherapy, including laser photocoagulation, cryotherapy, plaque radiotherapy, or external beam radiotherapy, was not delivered unless there was documented tumor recurrence, then these methods were used; after stable follow-up, ophthalmic oncology examinations were repeated at 3 months, 4 months, and then every 6 months thereafter. Magnetic resonance imaging of the brain and orbit were performed twice yearly until age of 5 years.

Technical Difficulties:

The procedure of Intra-ophthalmic artery melphalan technique was performed successfully in most IAC attempts. Only Two attempts to cannulate the ophthalmic artery failed due to narrow diameter, and melphalan was then delivered in the origin of the artery in one patient, after confirmation of the microcatheter flow towards the eye globe with angiography and via anastomosis with middle meningeal artery in the other patient.

Only two events of transient spasm of the ophthalmic artery were observed as revealed by post-procedural angiography. Such complication was solved with nimodipine infusion and did not alter vision. No cardiopulmonary events occurred, and no complications in the injection site of the femoral artery were observed.

Results

Statistical analysis was performed for 26 patients with 30 intra ocular retinoblastoma group D and E, 14 males (54%) and 12 females (46%). Their ages ranged from 5 months to 24 months with a mean age of 16 months. They all received IAC of melphalan alone. Among them, there were 22 cases (84.6%) of unilateral RB and 4 cases (15.4%) of bilateral RB. For patients with bilateral RB, both eyes were treated with IAC therapy as our selected bilateral cases were assigned to either Group D or Group E according to the International Classification of RB (ICRB) and offered IAC as an alternative treatment to enucleation.

The initial clinical presentations of RB included leukocoria (n=19, 63.4%), strabismus (n=4 eyes, 13.3%), and reduced visual acuity (n=7, 23.3%). Group D represented 66.7% (n=20) and group E represented 3 3 .3% (n=10).

In most of our cases secondary IAC was delivered after failure of previous intravenous chemoreduction, presenting as recurrence of solid tumors with mean tumor diameters for group D and E RB were 19mm and 21mm respectively, vitreous seeds were present in 14 cases from group D and 6 cases from group E, sub retinal seeds were found in 14 cases from group D and 5 cases from group E, and finally subretinal fluid affection were found in 15 cases from group D and 5 cases from group E (Table 1).

The systemic chemotherapy cycles of the 30 RB before IAC were 4 cycles (n=8), 5 cycles (n=8), 6 cycles (n=10), and more than 6 cycles (n=4). The mean chemotherapy cycles were 5 cycles.

On average, each eye received 3 OAC treatments (median 3, range 2 to 4 cycles). After completion of IAC treatment regimens for our patient's clinical outcomes were as follows:

In group D retinoblastoma: We achieved the following results: Sub retinal seeds control 100% (14 out of 14 cases), vitreous seeds control 93% (13 out of 14 cases), sub retinal fluid control 86.6% (13 out of 15 cases) compared to group E retinoblastoma were sub retinal seeds control were

achieved in 100% (5 out of 5 cases), vitreous seed control 66.6% (4 out of 6 cases) and sub retinal fluid control 40% (2 out of 5 cases) (Table 2).

After completion of designed IAC treatment regimens for our patients the overall globe salvage rates were 95% (19 out of 20) in group D retinoblastoma versus 30% (3 out of 10) in group E retinoblastoma.

For group D retinoblastoma, complete response was achieved in 30% of RB (n=6 out of 20 lesions), very good partial response (VGPR) accounted for 35% (n=7 out of 20 lesions), partial response represented 30% (n=6 out of 20 lesions) and finally no response represents 5 % (n=1 out of 20 lesions).

For group E retinoblastoma, no cases achieved complete response 0%, very good partial response (VGPR) accounted for 10% (n=1 out of 10 lesions), partial response represented 20% (n=2 out of 10 lesions) and finally no response represents 70% (n=7 out of 10 lesions) (Table 3).

The complications of treatment are listed in Table (4). Short term ocular adverse events included eyelid edema (n=15, 50%), bulbar conjunctiva congestion (n =7, 23.3%), mild ptosis (n=5, 16.7%) and long term complications included ophthalmic artery spasm with reperfusion (n=2, 6.7%) retinal atrophy (n=1, 3.3%). Most of adverse ocular events were resolved spontaneously. No severe systemic adverse events, such as stroke or sepsis, or severe local adverse events, such as cranial nerve palsies, were observed. Ten patients experienced fever (not exceeding 38.5ºC) following treatment, and transient vomiting occurred in sixteen patients.

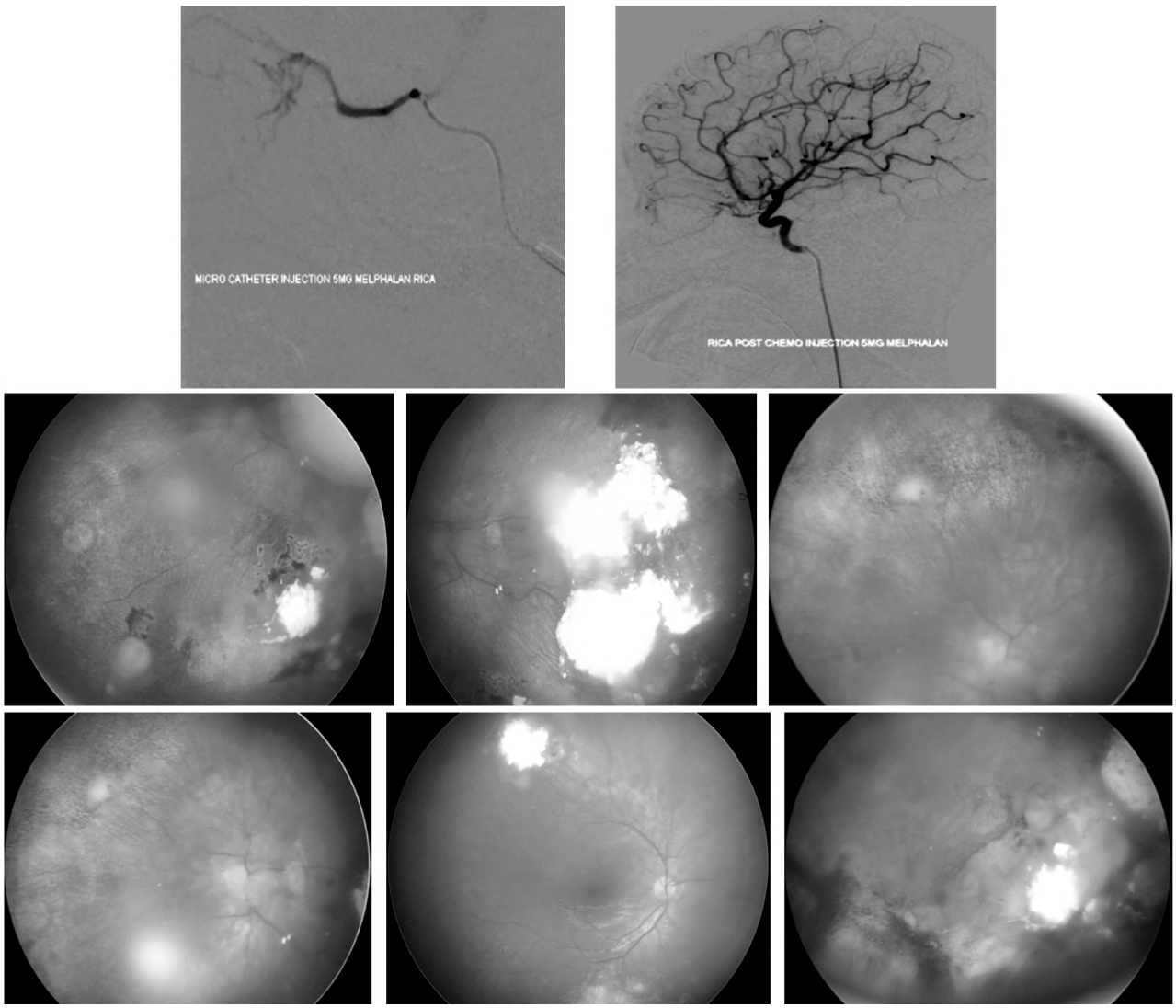

Fig. (1): Male patient 24 months old. Clinical presentation leukocoria, no squint. Age at first presentation: 9 months. No history of inheritance. Right eye group D retinoblastoma with Vitreous seeds & subretinal seeds maximal diameter 7.5mm. RETCAM wide viewing angle images showing diffuse vitreous seeds with macular tumor partially calcified. Active seeds were resistant after repeated chemotherapy and TTT. After 3 sessions IAC tumor regressed with calcified seeds. Follow-up for 12 months revealed inactive calcified seeds.

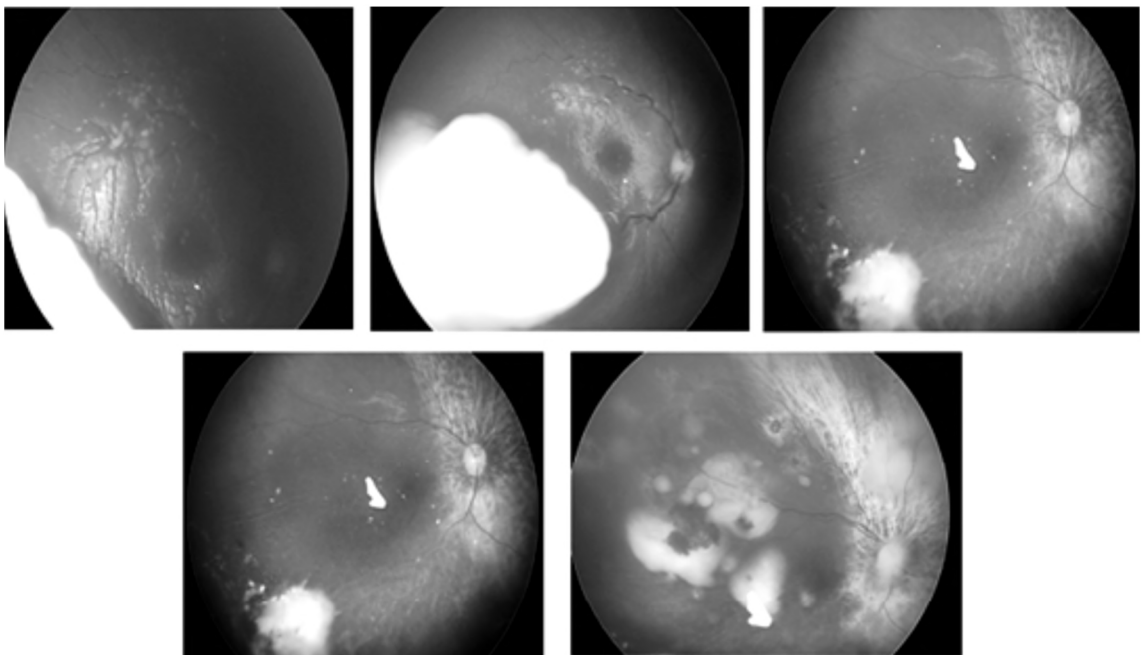

Fig. (2): Male patient 24 months old with unilateral retinoblastoma in the right eye. Clinical presentation leukocoria, no squint. Age at first presentation: 16 months. No history of inheritance. Right eye group D retinoblastoma with vitreous seeds & subretinal seeds maximal diameter 12mm treated with 5 cycles systemic chemotherapy. RETCAM wide viewing angle images showing OD inferotemporal mass with diffuse seeds. Regressed mass with calcified seeds centrally and active ones inferiorly following IAC injection. Follow-up revealed multiple new masses with hemorrhage and diffuse active seeds (recurrence) with decision of enucleation.

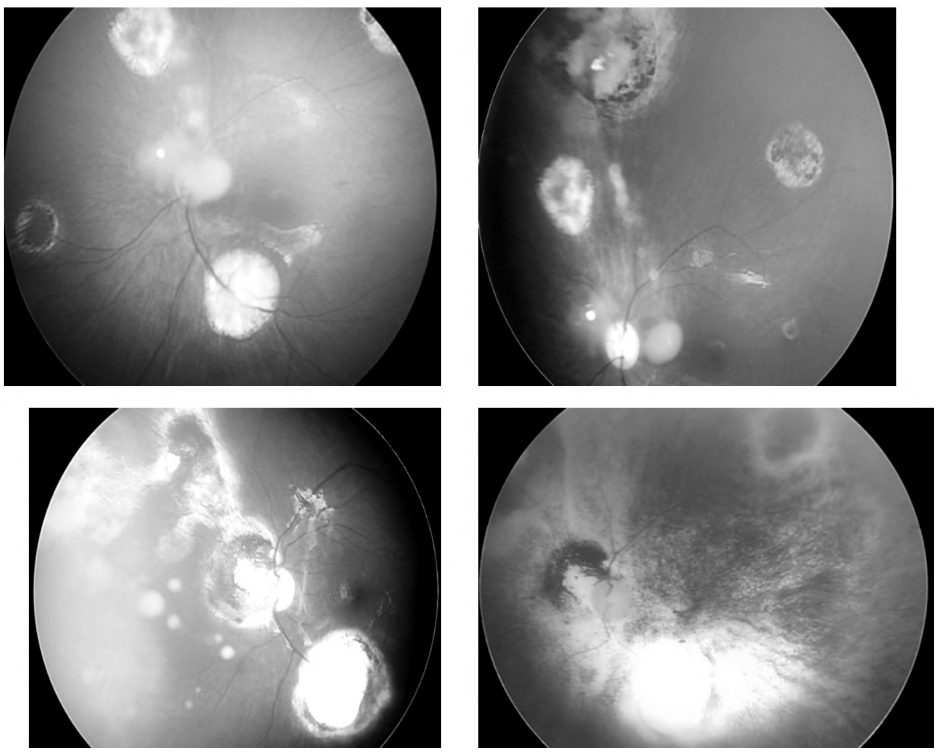

Fig. (3): Male 6-month-old with unilateral group D retinoblastoma was treated via intra-arterial chemotherapy after failure of previous intravenous chemoreduction. After seven cycles of intravenous chemoreduction, the tumor had failed to respond adequately to a standard systemic chemotherapy. Fundus appearance of the same eye after three intra-arterial chemotherapy procedures shows a calcified tumor. Follow-up for 14months revealed stable calcified tumor.

Table (1): RB demographics in our study.

ICRB	Mean tumor diameter in mm	Sub retinal seeds	Vitreous seeds	Subretinal fluid	IAC medic-ations
D=20	19	14	14	15	Melphalan (20)
E=10	21	5	6	5	Melphalan (10)

Table (2): Tumor control after completion of IAC.

ICRB	Sub retinal seeds control	Vitreous seeds control	Subretinal fluid control	Globe salvage
D=20	14 (100%)	14 (100%)	13 (86.6%)	19 (95%)
E=10	5 (100%)	5 (100%)	2 (40%)	3 (30%)

Table (3): Treatment outcome after completion of IAC.

ICRB	Complete response CR	Very good partial response VGPR	Partial response PR	No response	Globe salvage
D=20	6 (30%)	7 (35%)	6 (30%)	1 (5%)	19 (95%)
E=10	0 (0%)	1 (10%)	2 (20%)	7 (70%)	3 (30%)

Table (4): The treatment complications of intra-arterial chemotherapy for Retinoblastoma in 30 eyes.

Adverse ocular complications	Number of eyes (%)
Eyelid edema	19 (95%)
Bulbar conjunctiva congestion	3 (30%)
Mild ptosis	5 (16.7%)
Ophthalmic artery spasm	2 (6.7%)
Retinal atrophy	1 (3.3%)
Systemic adverse events	**Number of patients**
Fever	10 (38.5%)
Transient vomiting	16 (61.5%)

Discussion

RB had been a disease leading to blindness and death in children [6]. Complete tumor control with systemic chemotherapy has been achieved in 100% of the eyes of Group A, 93% of Group B, 90% of Group C, 47% of Group D, and 33% of Group E according to ICRB [7].

Many of the group D eyes in database, particularly those evaluated before 1994, were managed with enucleation, but more recently, IVC and IAC have generally been employed. Globe salvage for group D eyes can approximately achieve with IAC 90% of properly selected cases, and enucleation can possibly be avoided. Most group E eyes have been and continue to be managed with enucleation, particularly because of relatively poor control with chemotherapy (IVC and IAC) and risks for metastatic disease according to Shields et al., [8].

The results of Shields et al., were matching our study results where eye preservation rates were 95% (19 out of 20) in group D retinoblastoma and only 30% (3 out of 10) in group E retinoblastoma.

In our study, from 20 group D retinoblastoma, only one didn't responded to IAC (5%), complete response was achieved in 6 RB (30%), 7 RB achieved very good partial response (VGPR) (35%) and finally 6 RB achieved partial response (30%)

While for group E retinoblastoma, results were totally different; no cases achieved complete response 0%, only one RB achieved very good partial response (VGPR) (10%), 2 RB achieved partial response (20%) and finally 7 RB didn't respond to IAC treatment (70%). Therefore, careful patient selection for IAC would be warranted and eyes with advanced refractory Group E should be considered for enucleation (Table 3).

IAC was initially developed for treating children with unilateral RB who need enucleation as the first-line therapy. Subsequent reports showed that IAC may be applied as the second line of therapy for refractory RB, following failure of other treatments including intravenous chemotherapy and other focal therapies [9].

Many authors observed that primary IAC had better outcomes in terms of globe salvage, tumor control, and functional outcomes as compared to secondary IAC. Abramson et al., reported better 2 year probability of ocular salvage with primary IAC (64%-83%) as compared to secondary IAC (50%-76%) [10]. In our study only one case underwent IAC as primary line of treatment for Group D RB which achieved very good partial response of the tumor with 3 cycles of IAC respectively, with stable tumor at subsequent follow-up however we couldn't generalized this result due to small number of patients included in this category in our study.

Chen et al., [11] aimed to determine the factors influencing clinical outcomes of IAC and found that the globe salvage of IAC was significantly associated with tumor staging and previous treatment. The slightly reduced IAC control when it was applied as second-line therapy could be related to relative chemotherapy resistance with the anti vascular effect of chemotherapeutic agents [12]. In contrast to the Chen et al., study results, about 94.7% of group D RB (18 out of 19) in our study, treated with secondary IAC responded adequately to intra arterial melphalan injection with only one RB 5.3% that failed to respond to primary systemic chemotherapy and secondary IAC with follow-up

revealed multiple new masses with hemorrhage and diffuse active seeds (recurrence) with decision of enucleation.

In treatment of RB resistant to chemotherapy, melphalan sometimes combined with topotecan was administered to enhance effectiveness. Melphalan is a powerful alkylating agent whose applications in pediatric oncology have been limited because of its severe bone marrow toxicity with systemic administration. However, melphalan has been demonstrated to be one of the most effective drugs against retinoblastoma [13]. Furthermore, i ntravitreal injection of melphalan and/or ocular hyperthermia have been associated to treat vitreous seeding. This technique resulted in common anaesthesia related adverse events (particularly bradycardia); however, no deaths or strokes were reported [14].

Abramson et al., in 2008 reported the successful preliminary results of a novel technique of superselective ophthalmic artery infusion of chemotherapy. The treatment was relatively safe and repeatable. The strategy of direct infusion into the ophthalmic artery allows the delivery of high concentrations of chemotherapy to the eye and the tumor, with far lower concentrations to the patient than systemic administration. It has been proposed to define this technique as 'super-selective chemosurgery, because of the cannulation of a small artery such as the ophthalmic artery. The maximum actual dose per treatment is considered to be 6 mg/ml, because periocular oedema and measurable neutropenia have been encountered at a dose of 7.5mg [15].

There has been no standard number of cycles for the IAC delivery. One study indicated that complications from one or two cycles of IAC were mostly transient and incidences of eyelid edema and ptosis [16]. The investigators concluded that one or two cycles of IAC could be sufficient for tumor control in selected eyes from Group C or Group D. However, Trinavarat et al., demonstrated that IAC could be performed safely for as many as 15 sessions without severe systemic adverse events. However, the cumulative irradiation exposure from fluoroscopy during the procedure should be concerned. The estimated irradiation dose in a single IAC procedure was 0. 1 6Gy to the treatment eye, which, in accumulated doses, could be cataractogenic and possibly carcinogenic, especially for irradiation-sensitive patients with RB. Hereby, the eyes received treatments with two to four cycles, and reperfusion may increase the risk of vasospasm [17].

In our case series patients received two to four IAC cycles per lesion with average of 3 cycles. Most of adverse ocular events in our study were resolved spontaneously, with only two cases complicated with transient spasm of the ophthalmic artery were observed and were solved with nimodipine infusion and did not alter vision and one case with irreversible retinal atrophy and no severe systemic effects were encountered (Table 4).

Conclusion:

IAC is very effective treatment for ICRB group D retinoblastoma either as a primary or secondary line of treatment, and appears to achieve high rates of globe salvage, without compromising patient survival. The procedure can be performed safely multiple times, using multiple intra-arterial chemotherapeutic agents, and allows the vast majority of children to keep their eyes. However, it should be cautioned for Group E RB as its results is still doubtful.

References

1- REESE A.B., HYMAN G.A., TAPLEY N.D. and FORREST A.W.: The treatment of retinoblastoma by X-ray and triethylene melamine. AMA. Arch. Ophthalmol., 60: 897-906, 1958.

2- ABRAMSON D.H., DUNKEL I.J., BRODIE S.E., KIM J.W. and GOBIN Y.P.: A phase I/II study of direct intraarterial (ophthalmic artery) chemotherapy with melphalan for intraocular retinoblastoma initial results. Ophthalmology, 115: 1398-404, 1404.e1, 2008.

3- KUNKELE A., JURKLIES C., WIELAND R., LOHMANN D., BORNFELD N., EGGERT A., et al. Chemoreduction improves eye retention in patients with retinoblastoma: A report from the German Retinoblastoma Reference Centre. The British Journal of Ophthalmology, 97 (10): 1277-83. doi: 10.1136/bjophthalmol-2013-303452 PMID: 23863458, 2013.

4- VAJZOVIC L.M., MURRAY T.G., AZIZ-SULTAN M.A., SCHEFLER A.C., WOLFE S.Q., HESS D., et al.: Superselective intraarterial chemotherapy: EValuation of treatment-related complications in advanced retinoblastoma. Clinical Ophthalmology, 5: 171-6. doi: 10.2147/OPTH. S12665 PMID: 21 383945; PubMed Central PMCID: PMC30 45066, 2011.

5- CHEN M., ZHAO J., XIA J., LIU Z., JIANG H., SHEN G., et al.: Intra-arterial chemotherapy as primary therapy for retinoblastoma in infants less than 3 months of age: A Series of 10 case-studies. PLoS One, 11: e0160873, 2016.

6- AGGARWAL H. and KUMAR P.: Orbital retinoblastoma: Prosthetic frontier. J. Cancer. Res. Ther., 11: 1047, 2015.

7- SHIELDS C.L., RAMASUBRAMANIAN A., THANGAPPAN A., HARTZELL K., LEAHEY A., MEADOWS A.T., et al.: Chemoreduction for group E retinoblastoma: Comparison of chemoreduction alone versus chemoreduction plus low-dose external radiotherapy in 76 eyes Ophthalmology, 116: 544-510, 2009.

8- SHIELDS C.L., ALSET A.E., SAY E.A., et al.: Retinoblastoma control with primary intra-arterial chemotherapy: Outcomes before and during the intravitreous chemotherapy era. The Paul A Chandler M.D. Lecture, 2014.

9- FABIAN I.D., ONADIM Z., KARAA E., DUNCAN C., CHOWDHURY T., SCHEIMBERG I., et al. The management of retinoblastoma. Oncogene, 37: 1551-60, 2018.

10- ABRAMSON D.H., DANIELS A.B., FRANCIS J.H., BRODIE S.E., DUNKEL I.J., MARR B.P., et al.: Intra-arterial chemotherapy (ophthalmic artery chemosurgery) for group d retinoblastoma. PLoS One, 11: e0146582, 2016.

11- 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., 95: 613-8, 2017.

12- SHIELDS C.L., SAY E.A., POINTDUJOURLIM R., CAO C., JABBOUR P.M., SHIELDS J.A., et al.: Rescue intra-arterial chemotherapy following retinoblastoma recurrence after initial intra-arterial chemotherapy. J. Fr. Ophtalmol., 38: 542-9, 2015.

13- INOMATA M. and KANEKO A.: Chemosensitivity profiles of primary and cultured human retinoblastoma cells in a human tumor clonogenic assay. Jpn. J. Cancer Res., 78: 858-868, 1987.

14- UEDA M., TANABE J., INOMATA M., KANEKO A. and KIMURA T.: Study on conservative treatment of retinoblastoma-effect of intravitreal injection of melphalan on the rabbit retina. J. Jpn. Ophthalmol. Soc., 99: 1230-1235 (in Japanese), 1995.

15- ABRAMSON D.H., DUNKEL I.J., BRODIE S.E., KIM J.W. and GOBIN Y.P.: A phase I/II study of direct intraarterial (ophthalmic artery) chemotherapy with melphalan for intraocular retinoblastoma initial results. Ophthalmology, 115: 1398-1404. 1404.e139, 2008.

16- PETERSON E.C., ELHAMMADY M.S., QUINTERO-WOLFE S., MURRAY T.G. and AZIZ-SULTAN MA.: Selective ophthalmic artery infusion of chemotherapy for advanced intraocular retinoblastoma: Initial experience with 17 tumors. J. Neurosurg, 114:1603-8, 2011.

17- TRINAVARAT A., CHIEWVIT P., BUABOONNAM J., SANPAKIT K. and ATCHANEEYASAKUL L.O.: Selective ophthalmic arterial infusion of chemotherapeutic drugs for recurrent retinoblastoma. J. Pediatr. Hematol. Oncol., 34: e218-21, 2012.

دور الحقن الشريانى للعلاج الكيمائى فى علاج أورام الشبكية المتقدمة مجموعة (ج) و(ه)

يعد الحقن الشريانى للعلاج الكيمائى إستراتيجية فعالة لعلاج إورام الشبكية. فهذه التقنية تستخدم كعلاج أولى وعلاج ثانوى. ونظراً لكونها تقنية آمنة ذو فعالية عالية فمن المتوقع أن يحل الحقن الشريانى للعلاج الكيمائى محل إستراتيجيات العلاج التقليدية بل وسوف تصبح خيار العلاج الأول حتى بالنسبة للأورام الشبكية القابلة لإستراتيجيات العلاج الأخرى.

وكما هو الحال مع إدخال أى طرق علاج جديدة، فإن الدراسات تبين أن المضاعفات التقنية تتناقص مع تقدم العلم والخبرة المتزايدة فى مجال الأشعة التداخلية مما سيودى إلى تحقيق معدلات نجاح أعلى والتحكم الفائق فى الورم.

فقد سمحت تقنية الحقن الشريانى للعلاج الكيمائى بالعيون التى كام من الممكن إزالتها فى الماضى ليتم إنقازها، وتمكن الغالبية العظمى من مرضى أورام الشبكية المجموعة د من الأحتفاظ بعيونهم. ولكن يتطلب الأمر الكثير من الأبحاث فى محاولة تحسين نتائج الحقن الشريانى للعلاج الكيمائى فى علاج أورام الشبكيةالمجموعة ه لأن نتائجها لا تزال قليلة مما يتطلب إستئصال العين المصابة.