CASE SERIES

Experience of selective intra-arterial chemotherapy for Retinoblastoma

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Abstract

This study determined the outcomes of selective intra-arterial chemotherapy (IAC) for the treatment of Retinoblastoma in Pakistan. Single centre, prospective, interventional case series of three consecutive eyes were diagnosed as unilateral Retinoblastoma. Patients underwent IAC with Melphalan (0.5mg/kg) at Lahore General Hospital from July 2017 to January 2018. Selective ophthalmic arterial infusion was carried out in all 3 cases. Patients were evaluated on 1st, 3rd and 10th post-operative day and then at 4 weeks interval, till date. Among three eyes, 2(66.6%) were of stage C and 1(33.3%) of stage D. After 3 cycles of intra-arterial chemotherapy, full regression of the lesion was observed in all the eyes (100%). Complete regression and calcification of tumour was seen in 1 (33.3%) eye at 1 month post-treatment and 2 eyes at 2 months post-treatment. Globe was preserved in all 3 (100%) cases. Notable complications included eyelid oedema, orbital congestion and skin hyperaemia. None of the patients had any systemic side effects. Intra-arterial chemotherapy (IAC) is an effective modality for the treatment of Retinoblastoma and it plays a cardinal role in preservation of integrity of the globe.

Keywords: Retinoblastoma, intra-arterial infusion, ophthalmic artery, cancer chemotherapy.
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Introduction

Retinoblastoma (RB) is the most common intraocular malignancy of childhood[1] with frequency of 1:17000 live births.[2] There is a strong genetic predisposition for this disease with 13q14 translocation being the key mutation.[3] Approximately 60% of cases are bilateral while 40% are unilateral.[4] With respect to gender distribution, there is male predominance 1.2:1 with survival rate ranging from 86-92%.[5] Retinoblastoma is diagnosed in patients at an average age of 18 months, with 90% cases diagnosed younger than 5 years of age.[6]

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With recent advances in research and clinical trials, there has been a paradigm shift in the treatment protocols of Retinoblastoma. Selective systemic chemotherapy including intra-venous (IV) and intra-arterial (IA) route, localized chemotherapy i.e. intra-vitreal delivery, cryotherapy and laser photocoagulation are now gaining popularity.[7] Malphalan is one of the chemotherapeutic agents used in the treatment of Retinoblastoma. It is an alkylating nitrogen mustard that acts through alkylation of the DNA nucleotide guanine and causes linkages between strands of DNA. Recommended dose for intra-arterial route is 0.5mg/kg.[8]

In 1958, Reese et al.[9] demonstrated chemotherapy delivery in carotid artery for the first time that led to intra-arterial chemotherapy (IAC) for Retinoblastoma which showed promising results. Several years later in 1966, a study was conducted in Japan demonstrating favourable results of 5-fluorouracil injection into the supraorbital artery of patients with Retinoblastoma.[10] In 1980s, Melphalan was chosen as the most effective and potent drug among many chemotherapeutic agents for the treatment of Retinoblastoma. Melphalan showed a tremendous decrease in colony formation of primary Retinoblastoma cells.[11] In a study, Kaneko et al.[12] managed 6 patients having Retinoblastoma by 40 mg of intra-arterial Melphalan with success in only 2 patients but with remarkable systemic side effects, particularly myelosuppression and alopecia. In order to lessen the systemic side effects of chemotherapeutic agents, a study was conducted from 1989 to 1999 with an aim of providing selective and focal delivery of drug. Internal carotid artery was occluded with a balloon distally and an injection with a lower dose of chemotherapeutic agent (5-10 mg/m^2) was administered to minimize the systemic side effects.[13] Their report was published in 2004, which mentioned lower side effects with a non-selective technique as higher concentrations of drug was received by cavernous branches of internal carotid artery.[13]

In 2011, a study of selective ophthalmic artery catheterization and an injection of Melphalan was

conducted among 95 eyes and it was concluded that IAC is safe and an effective method in the treatment of advanced intraocular retinoblastoma.[15] The Kaplan-Myer estimates of ocular event-free survival rates at 2 years in their study was 70.0% (95% confidence interval = 57.9 - 82.2%) for all the eyes.[14] Shields et al.[15] published a report of outcomes of IAC for Retinoblastoma and concluded that preservation of eyeball was seen in 72% of the primary-treated cases and in 62% of the secondary-treated cases.

Case Report

This was a single centre, prospective, interventional case-series. The study was conducted at Lahore General Hospital, Lahore with the collaboration of Ophthalmology and Neuro-radiology departments from July 2017 to January 2018. Three consecutive eyes of 3 patients (n=3) with RB who underwent intra-arterial chemotherapy using Melphalan were included in the study. Approval from the Institutional Review Board was taken for this study. Informed consent was obtained from all the participants and a proforma was designed to collect the data of patients including name, age, gender, laterality, stage of disease and any history previous treatment. Interventional radiologist performed the intra-arterial chemotherapy in the operating theatre under general anaesthesia. The study followed the tenets of Declaration of Helsinki.

Examination under anaesthesia (EUA) was done with the documentation of clinical findings including laterality, stage of disease, total number of lesions, intraocular pressure (Tonopen) with findings of anterior and posterior segments. Magnetic Resonance Imaging scan and a B scan was performed in all the patients after EUA. Certain investigations including complete blood counts (CBC), chest X-ray, liver function tests, renal function tests, serum calcium, magnesium, potassium and basic coagulation tests were conducted at baseline and repeated at 2 weeks intervals. Tumour and other retinal findings were documented by retinal drawings and fundus pictures with retinal camera (MII Ret Cam, India).

After taking consent from the parent or a legal guardian, intra-arterial chemotherapy was delivered by the interventional radiologist in a neuro-angiography suite under general anaesthesia. State of anticoagulation was achieved by intravenous heparin (75 IU/kg) as described in other studies. After adequate exposure, the groin area was draped with 5% povidone iodine; femoral artery region was selected to place a 4-French arterial sheath. Under fluoroscopic guidance, the French (1.3-mm-diameter) catheter was guided into the ipsilateral internal carotid artery. Ocular and cerebral vasculature including the path of the ophthalmic artery from the internal carotid artery was visualized adequately by taking serial arteriograms (Figure-1a). 450-?m micro-catheter with fluoroscopy was used to catheterize ipsilateral ophthalmic artery and a confirmatory angiogram was then taken (Figure-1b). Chemotherapeutic agent (Melphalan) was infused at a dose of 0.5mg/kg in a pulsatile fashion over 30 minutes (Figure-1c). After infusion, a confirmatory angiogram was taken again to look for vasospasm (Figure-1d). In all the cases, 3 cycles of IAC were administered at 4 weeks intervals. After the completion of the procedure, catheters were removed, femoral sheath was withdrawn and manual compression of femoral artery was done to achieve haemostasis. After observing for 6 hours, child was discharged on the same day. Sterilization of wound was achieved by sterile dressing for 2 days and topical antibiotic ointment application.

Throughout the study period, same standard techniques were used. Patients were followed-up at 1st, 3rd and 10th post-op day and then at 4 weeks interval, till date. Intra-arterial chemotherapy was repeated at 4 weeks intervals. Patency of ocular vasculature was assessed. Retina and optic nerve head was evaluated by examining the fundus by indirect ophthalmoscopy. Treatment outcomes were

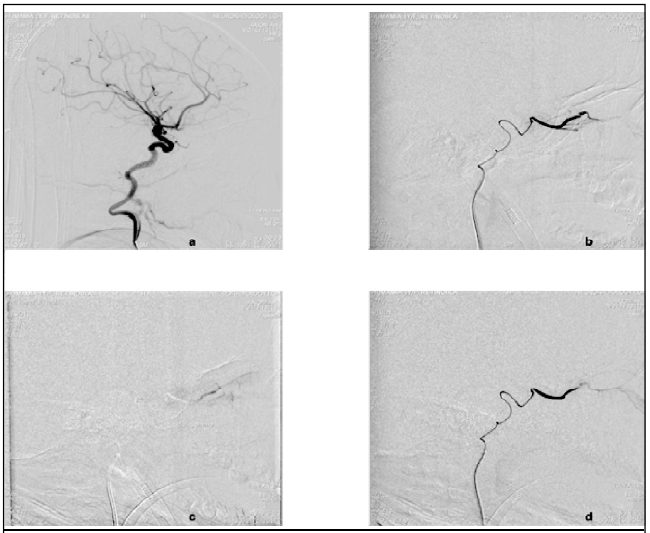

Figure-1: a) Injection of dye in the internal carotid artery. b) Selective ophthalmic artery catheterization before IAC. c) During the injection of chemotherapeutic agent (Melphalan). d) after the chemotherapy procedure.

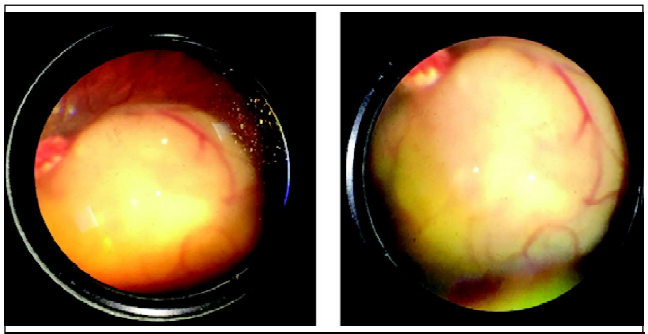

Figure-2: Pre-treatment fundus photograph of the lesion.

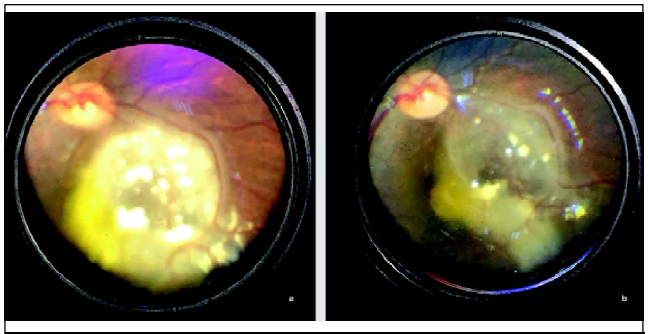

Figure-3: a) 4 weeks post-treatment fundus photograph of the lesion. b) 6 months post-treatment fundus photograph of the lesion.

shown in terms of reduction in vitreous seeding, tumour calcification, preservation of anatomy of the globe and complications of the procedure.

A total of 3 eyes from 3 patients were examined and treated. Male 2(66.6%) predominance was noted over females 1(33.3%). Two (66.6%) of the patients were in 7-12 months age group and one (33.3%) in 13-24 months of age. Two (66.6%) patients presented with leukocoria and one (33.3%) had red eye. International classification of retinoblastoma[16] was used to assess the stage of the disease. Among three eyes, 2 (66.6%) were of stage C (n = 2) and 1 (33.3%) of stage D (n = 1). After treatment with intra-arterial chemotherapy, full regression of the lesion was observed in all the eyes (100%). Calcification of the tumour was seen in 1 (33.3%) eye at 1 month post-treatment and 2 eyes at 2 months post-treatment. No vitreous seeding was observed in any of the cases at 6 months follow-up. Globe was preserved in all 3 (100%) cases. At first day of follow up, all of the cases (100%) showed lid oedema, 1 (33.3%) revealed orbital congestion, 1 (33.3%) had hyperaemia on the skin at the territory of supraorbital artery while none of the eyes showed ocular motility restriction, vascular accidents or systemic side effects. Figure-2 and 3 shows pre-treatment and post-treatment fundus photographs of a patient with group D retinoblastoma. Summary is given in Table.

Discussion

The incidence of Retinoblastoma in Pakistani population varies according to the region. In one study, the annual crude incidence of Retinoblastoma in Karachi was found to be 4.0/100,000 and 2.4/100,000 in children under the age of 5 and 10 years respectively.[17] In another study from Pakistan, late presentation, advanced stage with male predominance was reported; hereditary patterns were found to be 40%.[18]

With the passage of time and recent advances, management options of Retinoblastoma have revolutionized the outcomes in term of globe salvage and reduction in disease process. Targeted treatment of Retinoblastoma is gaining popularity with an aim of adequate drug availability at the tumour site.[9] Chemotherapy, radiotherapy, focal treatments like cryotherapy, thermotherapy and laser photocoagulations are current treatment strategies. There are different treatment modalities to deliver chemotherapy i.e. by intravenous, intra-arterial, sub-tenon's and intravitreal routes.[19]

In our study intra-arterial chemotherapy (Malphalan) revealed tremendous results regarding preservation of anatomy of the globe (100 %) and reduction in tumour growth as demonstrated by significant drop in vitreous seeding (100%) and calcification of tumour (100%). Abramson et al.[20] published a study in 2016 showing the efficacy of selective ophthalmic artery chemotherapy. Globe salvage was achieved in up to 70% according to Kaplan Meir estimate even in advanced disease (Stage D, E).

Another study showed regression (73%) of Group D and

Table: Summary of the data.

Age at diagnosis (months)	Gender	Laterality	Disease Classification	Status of fellow eye	Treatment prior to IAC	Disease after IAC	Adverse effects
9	Male	Unilateral	C	Normal	Nil	No vitreous seeds, tumour calcified	Lid oedema, orbital congestion
12	Female	Unilateral	C	Normal	Nil	No vitreous seeds, tumour calcified	Lid oedema
21	Male	Unilateral	D	Normal	Nil	No vitreous seeds, tumour calcified	Lid oedema, Skin Hyperaemia

E tumours treated with intra-arterial chemotherapy; reduction in Vitreous/subretinal seeding was achieved in 80% of the cases.[21] The staging of tumour at baseline has a significant bearing on the overall outcomes. Functional outcomes with globe salvage following intra-arterial chemotherapy was addressed in a study and concluded that if intra-arterial chemotherapy is used as primary rather secondary therapy, it can significantly preserve the anatomy of the globe.[15]

As modality of intra-arterial chemotherapy is very beneficial, it certainly has fewer side effects including lid oedema, orbital congestion, blephroptosis, ocular motility restriction, myelosupression, vasospasm, alopecia, nausea and vomiting.[22] In our study, only lid oedema, orbital congestion, vasospasm and skin hyperaemia were noticed. No systemic toxicities were observed. Lee et al.[23] compared the side effects of intravenous chemotherapy and selective ophthalmic artery chemotherapy which showed that the IAC is associated with minimum systemic side effects ($p< 0.05$) as compared to conventional intra venous chemotherapy.

Intra-arterial chemotherapy for RB have fewer limitations, it is technically challenging, requires specific set of skills and equipment and is a costly procedure. On the other hand, it is very beneficial as it is a precise and effective technique which helps in reducing the dosage of chemotherapeutic agents required for regression of RB and is an amazing modality for eyeball preservation.

This report describes the results of intra-arterial chemotherapy for RB for the first time in Pakistan. This study provides a better understanding of the efficacy and side effects of intra-arterial chemotherapy. Limit for total number of cycles of IAC needed is not determined yet but we have found 3 cycles satisfactory in our patients.

Before intra-arterial chemotherapy, intra-vitreal Malphalan showed promising results in reducing vitreous seeding but with the advent of IAC, we are probably better equipped with issues of vitreous seeding and globe salvage can be achieved to a greater extent. Intra-arterial chemotherapy and intra-vitreal chemotherapy are complementary to one another.[24,25] In all of our cases, vitreous seeding completely regressed and we have not used intra-vitreal Melphalan in any of these patients.

Limitations of our study include small sample size and short follow-up period. With time and greater experience, number of our patients for this modality will be increased. Larger studies with longer follow-ups are needed to better understand the tumour response in the future.

Conclusion

In our early experience, we found out intra-arterial chemotherapy (IAC) to be an effective modality for treatment of retinoblastoma but further studies with larger number of patients and longer follow-ups are needed to better evaluate the effectiveness for this treatment strategy.

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Conflict of Interest: None to declare.
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