

Clinical patterns and outcomes of retinoblastoma in a tertiary care centre of a developing country

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Abstract

A retrospective study was conducted for which records of patients with Retinoblastoma (RB), treated at Lahore General Hospital between 2017 and 2021, were retrieved on February 1, 2022. Staging of RB, neuroimaging, RetCam images, and treatment were analysed. The study included 47 patients (22 females and 25 males). Mean age of presentation was 26.5 ± 15 months. Records of 84 eyes (37 bilateral and 10 unilateral) were examined. Family history was positive in only ($n=3$) 6.3% cases. Mean follow-up was 22.94 ± 14.4 months. Leucocoria was the commonest presentation, seen in 72 (85.7%) eyes, proptosis in 8 (9.5%), huge fungating mass in 2 (2.4%), while tumour was diagnosed because of screening in 2 (2.4%) patients. Post-treatment complications included cataract in two patients, Ischaemic chorioretinal toxicity, transient macular oedema, orbital oedema and transient intra cranial oedema in one patient each. Two patients had metastasis and underwent systemic chemotherapy. The study showed that patients with retinoblastoma can achieve better results if diagnosed early and treated with newer treatment options.

Keywords: Retinoblastoma, Proptosis, Chemotherapy, Melphalan.

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Introduction

¹Although the highest burden of Retinoblastoma (RB) is on developing countries, data shows that during the last 20 years, major contributions to the Retinoblastoma research has been made by the United States, China, and India.¹ The major cause of this great burden in Asia and Africa is due to the high birth rates recorded in these populations with limited resources for managing the disease.²

According to the World Health Organisation (WHO), Pakistan ranks sixth on the list of countries with high prevalence of RB.³ It is important to discern the clinical patterns of the disease, the treatment options, and their outcomes in Pakistan. Although there are some studies

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from Pakistan on Retinoblastoma, most of the work has been done on epidemiology, clinical presentation, and survival. Various studies address treatment with chemotherapy, cryotherapy, laser photocoagulation, enucleation, and exenteration; however, data related to Intra-arterial chemotherapy (IAC) and Intravitreal therapy with Melphalan and Topotecan (IVM and IVT) is scarce.

The purpose of presenting this data is to assess the disease pattern and response of treatment using all types of treatment options available in a tertiary care centre. There is special reference to the results of treatment using IAC, IVM, and IVT.

Patients and methods

Lahore General Hospital (LGH) is a tertiary care hospital in Punjab and is one of the main centres for treatment of Retinoblastoma in the city. The institutional review board approved the study (Ophthalmological Society of Pakistan-IRB; Approval #: OSP-IRB/2022/012 Date: 5.01.2022). Records of all RB patients who were treated at LGH from 2017 to 2021 were retrieved on February 1, 2022. This was a descriptive observation study and the retrieved data included city in which the patients reside, age at first presentation, presenting complaints, gender, laterality, family history, stage of tumour, tumour status after treatment, complications of treatment, and duration of follow-up. Verbal informed consent was taken from the parents of all patients for data collection and publication. All the patients who were diagnosed with RB at LGH were included in the study. Patients with incomplete data were excluded. Examination under anaesthesia was performed by an experienced ophthalmologist for diagnosis and staging of the disease. Magnetic resonance imaging (MRI) was performed in all the cases to check the spread of tumour into the brain. RetCam was used to record the images of tumour for later reference and to document the response to the treatment. Tests for genetic analysis of parents and siblings could not be performed due to unavailability of the facility at our centre. Staging of the disease was done according to the International intra-ocular retinoblastoma classification (IIRC).⁴ Depending on the stage, different treatment modalities were used, including laser photocoagulation, cryotherapy, enucleation, exenteration, local and systemic

chemotherapy. Intra-arterial chemotherapy (IAC) with Melphalan was given according to the patient's age as follows: 2.5 mg in patients less than one year of age, 3 mg in patients aged 1-2 years, 4 mg in patients aged 2-3 years and 5 mg in patients 3 years and above. Only one patient received 7 mg of Melphalan, which caused severe orbital oedema and pancytopenia. The procedure was performed under general anaesthesia. The common femoral artery was accessed by the neuro-interventional radiologist on the side of treatment. Ophthalmic artery was catheterised and Melphalan was injected. Intravitreal Topotecan was given in a dose of 0.3 mg in all cases. Intravitreal Melphalan (30µg) was also given in cases of vitreous seeding. Proper aseptic measures were taken and the drug was delivered through pars plana approach. After intravitreal injections, cryotherapy was applied to the site of injection to avoid seeding of tumour cells in the injection path. Enucleation was performed when there was no chance of saving the eye and if the tumour continued to grow despite local chemotherapy. Exenteration was done in case of orbital extension of the tumour. Systemic chemotherapy was carried out for metastasis. Histopathology was performed for the enucleated and exenterated eyes. Statistical analysis was done using IBM SPSS version 25. Descriptive statistics were used for gender, age, laterality, presenting complaints, treatment, and complications.

Results

A total of 47 patients of Retinoblastoma were treated at LGH from 2017 to 2021. Among these, 42 were from Punjab, three from KP, and two from Sindh. There were 22 females and 25 males with male to female ratio of 1:1.14. The mean age of presentation was 26.5±15 months (median= 24). Of the total of 84 eyes, 37 were bilateral and 10 unilateral

cases. Family history was positive in only 6.3%. Mean follow up was 22.94±14.4 months. Leucocoria was the commonest presentation (n=72 eyes, 85.7%), followed by proptosis in 8 (9.5%) cases, huge fungating mass in 2 (2.4%), and the tumour was diagnosed because of screening in 2 (2.4%) cases. The details of presentation of different grades of tumour and treatment are shown in Table.

Cataract developed in two patients, ischaemic chorioretinal toxicity, transient macular oedema, orbital oedema, and transient intra cranial oedema occurred in one patient each after treatment. The patient who developed transient orbital oedema had 7mg of IAC with Melphalan. However, he recovered 20 days after administration of the injection. In the intervening period he required admission and blood transfusion at the Paediatric oncology department. His vision improved when orbital oedema resolved and the eye started to open properly. Two patients had metastasis and underwent systemic chemotherapy.

Discussion

In this particular study, 95.7% patients were diagnosed before five years of age and 64% were diagnosed by the age of two years. This is very close to the figures reported by WHO, according to which, around 66% of Retinoblastoma patients are diagnosed before two years of age and 95% are diagnosed before their fifth birthday.³ According to the Global Retinoblastoma Group report, 85% patients of Retinoblastoma belonged to low and middle-income countries and leucocoria was the most common presentation.⁵ In our series also leucocoria was the most common presenting feature but the percentage was much higher (85.7%). Mean age of diagnosis in our series was 26.5 ±15 months (median=24). This was in contrast to the

Table: Clinical presentation and outcomes of retinoblastoma after treatment.

	A n (%)	B n (%)	C n (%)	D n (%)	E n (%)	Orbital n (%)	Total n (%)
Presentation							
Leucocoria	1(1.4)	25(34.7)	-	10(13.9)	36(50%)	-	72 (85.7)
Proptosis	1(12.5)	1(12.5)	1(12.5)	1(12.5)	-	4(50)	8 (9.5)
Huge fungating mass	-	-	1(50)	-	-	1(50)	2 (2.4)
Diagnosed as a result of screening	-	2(100)	-	-	-	-	2 (2.4)
Total number of eyes	2 (2.4%)	28 (33.33)	2 (2.4%)	11 (13.1)	36 (42.9)	5 (5.95)	84 (100)
Treatment							
Enucleation/ Exenteration	-	1(2.8)	-	2(5.6)	30(83)	3(8.3)	36 (42.9)
Intra-arterial Chemotherapy	-	14(63.6)	-	5(22.7)	3(13.6)	-	22 (26.2)
Intra-vitreous Melphalan	-	3(33.3)	2(22.2)	2(22.2)	2(22.2)	-	9 (10.7)
Intra-vitreous Topotecan	-	1(33.3)	-	1(33.3)	1(33.3)	-	3 (3.6)
Cryotherapy	1(100)	-	-	-	-	-	1 (1.19)
Laser photocoagulation	1(25)	3(75)	-	-	-	-	4 (4.76)
Systemic Chemotherapy	-	6(66.7)	-	1(11.1)	-	2(22.2)	9 (10.7)
Total treated	2	28	2	11	36	5	84 (100)
Regressed n (%)	2 (100)	27 (96)	2 (100)	9 (82)	6 (17)	-	46 (54.8)

A, B, C, D, E indicate grading based on International intra-ocular retinoblastoma classification.

patients from high-income countries who are diagnosed at the median age of 14 months.⁵ The reason is late presentation of patients in our part of the world.

In this particular study, 42.9% of the eyes were either enucleated or exenterated which is fewer than the earlier reported cases from Pakistan.⁶ This can be explained by the use of IAC, IVM, and IVT in our series, which were not used in previous studies. In another report by Chang et al, 47% of the cases underwent enucleation.⁷ They were followed-up for three years during which no recurrence was reported. Our follow-up was approximately two years and no recurrence was noted during this period. Before the start of IAC, IVM, and IVT, tumours of Group A were treated by focal lasers or cryotherapy, Group B, C, and D were treated by combination of lasers and chemotherapy. Enucleation was reserved for group E tumours and group D tumours not responding to chemotherapy. It was noted that IAC was very effective not only in early stages of the disease but also in group D and E as well.

Hundred percent globe salvage was described by Shields et al for group B and C eyes at five years.⁸ There is another report with 94% success for group D eyes, and $\leq 73\%$ even for the group E eyes with a combination of IAC and intravitreal chemotherapy.⁹ In the present study, these two modalities were not used in combination, rather they were used separately and the results were seen in the form of tumour regression in 100% of the cases during the two-year follow-up.

Three patients in our series with bilateral disease underwent systemic chemotherapy (six eyes). IAC was used in both eyes with 100% regression at two years.

The dose of IVM was kept at 30 μ g and major complications did not occur. Higher doses decrease enucleation rates but at the same time increased ocular toxicity. According to one report, one-unit increase in toxicity resulted in 31% reduction in enucleation.¹⁰ In contrast to that with lower doses, the results of tumour regression are compromised.

Limitations of this research are: retrospective study design, lack of gene analysis, and limited follow-up of two years.

Conclusion

This particular study discusses the effective use of Intra-arterial Chemotherapy, Intravitreal Melphalan, and intravitreal Topotecan. Timely use of these treatment

options can save eyes with Retinoblastoma, even in group D and E. Earlier treatment with external beam radiation resulted in disfigurements, which does not occur with the use of the above-mentioned therapies. Although the treatment is expensive, currently it is the treatment of choice for intraocular RB.

Retinoblastoma is a curable tumour, provided it is diagnosed early. The favourable results of our centre show that developing countries can have better treatment results by increasing awareness among the masses to get medical advice at an early stage. Further research needs to be done to develop new treatment options for tumours that are diagnosed at a late stage of the disease.

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