

## Treatment outcomes of retinoblastoma in children less than 6 months of age

### Abstract

**Objective:** To assess the results of children who have been diagnosed with retinoblastoma in less than 6 months of age in terms of globe saving and the need for chemoreduction (CRD).

**Material and Methods:** This is a retrospective study from 2018 to 2021 that includes 8 eyes of 4 infants. Of the 4 patients, 01 (25%) patient was male and 03 (75%) were females. All patients had bilateral disease with no positive family history. The 4 patients were classified according to the International Classification System for Retinoblastoma. Group A disease was diagnosed in 1 (12.5%) eye, Group B in 2 (25%), Group C in 1 (12.5%), Group D in 1 (12.5%), and Group E in 3 (37.5%) eyes. A performa was made that included; patient' name, date of birth, date of diagnosis, gender, laterality of retinoblastoma, family history, systemic chemotherapy agents used with the number of cycles and details of local therapy, complications, development of secondary malignancies and deaths. Primary outcome measures were the need for CRD and globe salvage.

**Results:** Three (75%) of the four infants having retinoblastoma in less than six months needed CRD to save their globes. 62.5 percent (5/8) of eyes had their globes saved, whereas three eyes (37.5 percent) were enucleated due to Group E illness. There were no CRD-related hospitalization and all patients survived.

**Conclusion:** collectively the targeted modalities and reduced-dose CRD, children having retinoblastoma with less than six months have more chances of globe saving comparable to those of older age groups. The saving of globe of two-thirds of the infants required CRD. A diagnosis of Group D or E in at least one eye initially or both eyes later on, increased the risk of requiring CRD ( $p$  0.0001 and  $p$  0.016, respectively).

**Key Words:** Retinoblastoma, 6 months of age, globe salvage, chemoreduction.

### Introduction

“Retinoblastoma is the most common primary intraocular malignancy in children with a prevalence of approximately one out of every 15,000–20,000 live births each year” [1]. “Intraocular retinoblastoma is diagnosed at an average age of 18 months; 12 months for bilateral disease and 24 months for unilateral disease. Many children are now diagnosed before they reach the age of three months due to the increased awareness among parents and physicians” [2, 3].

“These children having more chances to develop the inherited form of retinoblastoma, which increases their chances of developing numerous, bilateral tumours” [4,5]. Laser therapy, cryotherapy, or plaque brachytherapy are all options for infants diagnosed with low-grade tumours in the first three months of life. Advanced cancers used to necessitate external beam radiation (EBRT). Although high globe salvage rates were reported [6], “the short and long-term consequences of radiation in such young infants remain a concern”. “Secondary malignancies were observed to develop in addition to persistent facial deformities, with the highest occurrence rate in children treated with radiation during the first year of

life” [7]. As a result, clinicians switched to intravenous chemotherapy (IVC) for children who needed treatment during their first year of life.

“Systemic chemoreduction (CRD) has been used successfully in this age group all over the world, however there is need to know about its effectiveness in infant less than 6 months of age. This concern could be explained by the fact that small tumours in young children have lower vascular perfusion and drug delivery, as well as a higher risk of adverse effects, including an increased risk of hearing loss” [9–11].

“Depending on the clinical presentation, children having retinoblastoma in less than 6 months of age are treated with focal therapy, enucleation, and a proper dose of systemic chemotherapy. Patients diagnosed with Group A disease in one or both eyes initially are treated with focal modalities exclusively, according to the International Classification System for Retinoblastoma” [12]. “Local therapy can be used to treat a limited percentage of eyes with Group B disease with peripheral tumors (i.e. cryotherapy). CRD is used to treat the most of eyes having Group B disease and all eyes having Group C disease”. [17]

The laterality of Range D disease determines the treatment majority of people in this age group receive CRD.

Enucleation is frequently suggested for eyes with Group E illness. Chemotherapy for children under the age of six months consists of a three-drug regimen containing 50–75 percent of the entire dose of carboplatin, etoposide, and vincristine not administered to infants who are less than two months of age due to the risk of paralytic ileus.

We did analyses in retrospect manner of results of individuals having retinoblastoma in age less than 6 months who get treatment at Lahore General Hospital, Lahore, to assess the results of young infants having retinoblastoma who get treatment in the CRD period.

### **Material and Methods**

This retrospective chart study included 8 eyes of 4 babies, 01 (25 percent) male and /03 (75 percent) female, all with bilateral illness, from 2018 to 2021. Globe saving, the need for CRD, and the presence of treatment-related complications were the primary outcome measures.

patient had a MRI brain and orbits at their initial evaluation to rule out extraocular illness. For the diagnosis and classification of the condition, all patients underwent an anaesthetic examination that comprised the measuring of eye pressure, anterior segment examination, retinal examination in dilated eyes with scleral depression, and B-scan ultrasound. The International Classification System for Retinoblastoma was used to classify the eyes.

A performa was made that included; patient’ name, date of birth, date of diagnosis, gender, laterality of retinoblastoma, family history, systemic chemotherapy agents used with the number of cycles and details of local therapy, complications, development of secondary malignancies and deaths.

Enucleation was done for Group E disease in 3 out of 8 eyes (37.5%). 1 patient (25%) received only focal therapy for Group A disease in other eye while 3 (75%) received 6 cycles of chemotherapy (each cycle given 28 days apart) along with focal therapy as needed.

For patients under the age of six months, systemic chemotherapy included a reduced dose schedule that included a 50 percent reduction in all drugs for the first cycle. Due to theoretical concerns about paralytic ileus, vincristine is regularly omitted for patients under the age of two months [13]. Patients had follow up for intraocular tumour response and systemic toxicity after the first cycle of carboplatin, etoposide, and vincristine (or carboplatin and etoposide). Patients are retained on the 50 percent dose for the next cycle if there is a satisfactory tumour response but evidence of systemic drug toxicity. The dose is increased to 75 percent if there is inappropriate tumour response and no toxicity. Patients can be treated to a 100 percent dose of carboplatin, etoposide, and vincristine if all of these are following factors present: (1) having age greater than 3 months; (2) patient having no harm with the 75 percent dose, and (3) inappropriate tumour response to the 75 percent dose

Intravenous carboplatin 13 mg/kg (390 mg/m<sup>2</sup>) per day for two days, etoposide 5 mg/kg (150 mg/m<sup>2</sup>) per day for two days, and vincristine 0.05 mg/kg (1.5 mg/m<sup>2</sup>) on the first day only are the standard doses. We used  $\chi^2$  test for the association between baseline clinical characteristics and the need for CRD. The requirement for CRD was the primary endpoint in the regression analysis. Logistic regression was utilised in the univariate analysis to determine the significance of the need for CRD with each clinical category. To investigate the link between CRD and multivariate analysis, logistic regression analysis was used. The odds ratios, 95 percent confidence intervals, and p values were used to summarise the findings. The level of statistical significance was chosen at a 2-sided 5% level.

### **Results:**

From 2018 to 2021, 4 infants were diagnosed with intraocular retinoblastoma having less than 6 months of age took 8 eyes in this review. The average age of patients having retinoblastoma which we included in this review was 2.7 months (range 0–5 months).

Of the 4 patients, 01 (25%) patient was male and 03 (75%) were females. All patients had bilateral disease with no positive family history. The 4 patients were classified according to the International Classification System for Retinoblastoma. Group A disease was diagnosed in 1 (12.5%) eye, Group B in 2 (25%), Group C in 1 (12.5%), Group D in 1 (12.5%), and Group E in 3 (37.5%) eyes. Of the 4 infants diagnosed with intraocular retinoblastoma in less than 6 months of age, 3 (75%) required CRD in less than 6 months of age.

Globe saving was achieved in 62.5% (5/8) of eyes while 3 eyes (37.5%) were enucleated having Group E disease. No patient had drug toxicity. None was admitted for chemotherapy-related side effects. No death was recorded and none of the patient developed other secondary malignancies.

“We found a significant association between the International Classification grouping and the need for CRD ( $\chi^2$  test,  $p = 0.004$ ). For eyes classified as Groups A and B versus those classified as Groups C–E, there is no statistically significant association with the need for CRD ( $\chi^2$  test,  $p = 0.220$ ). However, eye classification as Groups A–C versus Groups D and E is significantly associated with the need for CRD ( $\chi^2$  test,  $p = 0.016$ ). [17]

### **Discussion**

In the CRD era, treating children who diagnosed with retinoblastoma in less than 6 months of age presents unique challenges for the ocular oncology team. Chemotherapy regimens are modified and local interventions are focused, due to the greater risk of systemic toxicity and complications in these

young infants. Abramson et al. [4] Children diagnosed early in life frequently present with extensive illness in one or both eyes, according to earlier research. In our study, 37.5 percent (3/8) of children's eyes diagnosed with Group E disease before the age of 6 months, which is similar to a previously reported series of older children [14,15]. Given their early age at the time of diagnosis, all of the patients had bilateral disease, which was to be expected. Advanced Group D and E disease, as well as bilateral disease, were connected to the need for systemic CRD ( $p = 0.016$  and  $p 0.0001$ , respectively).

"The management of newborns identified in less than 6 months of age in the CRD era appears to have improved globe salving and survival rates to those older reports of infants treated initially with radiation therapy" [4]. According to our findings, even in extremely young infants, a reduced-dose, 2- to 3-drug CRD regimen showed a high globe salvage rate with minimal medication toxicity.

In one study, seven patients treated with chemoreduction for Group D disease developed febrile neutropenia. The results were similar for side effects like hearing loss or development of secondary solid malignancy [16]. No patient was hospitalised for chemotherapy-related toxicity in our study. There were no secondary cancer related chemotherapy, indicating that avoiding radiation therapy prevents secondary cancers in this age group [3,4]. "We achieved 62.5% (5/8) globe salvage rate in our study. The results of our study are equivalent to standard dosage CRD in older age groups [15, 16], implying that concerns about tumour drug resistance with lower dose chemotherapy regimens in this younger group of patients may be unjustified". [17]

Patients who are diagnosed with advanced disease in one eye (Group D) and less advanced disease in the other eye (Group A,B) before the age of 6 months are the most challenging patients to treatment. In these cases, decision regarding focal therapy for the eye with less advanced disease must be made by the clinician in order to salvage the eye successfully. If not, CRD, which treats both eyes at the same time, is the recommended treatment option.

## Conclusion

Infants having retinoblastoma in less than six months of age are more likely to have disease in both eyes and are just as likely as older individuals to have severe disease. Treatment options include focal therapy, enucleation for advanced eyes, and a reduced-dose CRD programme with etoposide and carboplatin with or without vincristine and it's safer and manageable side effects. In retinoblastoma patients diagnosed before the age of six months, we report high eye salvage rates and low rate of long-term adverse effects with this treatment.

## Ethical Approval

This study has been approved by the hospital's ethical board committee.

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