Clinical outcomes of Group D Retinoblastoma at a tertiary care hospital in Pakistan

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Abstract

Purpose

To retrospectively analyse globe salvage rates in group D retinoblastoma (RB) with currently available treatment options in Pakistan over a period of nine years.

Methods

A retrospective, cross-sectional analysis including all patients who presented with Group D RB according to the International Classification of Retinoblastoma (ICRB), from April 2013 to December 2022 at Patel Hospital, Karachi, Pakistan. Indirect ophthalmoscopy done under anaesthesia was used to visualise and evaluate tumour characteristics and clinical response to the treatment offered. Globe salvage was attempted with systemic chemotherapy, local consolidative therapy along with intravitreal melphalan. Survival analysis was performed using Kaplan-Meier curves on SPSS version 26.

Results

The mean age at diagnosis was 17.2 months. 14 (93%) patients had bilateral disease and one (7%) had unilateral disease. Globe salvage was achieved in 11 out of 15 eyes (73.33%) in a mean follow up time of 57.5 weeks (range 7–263 weeks). All eyes received laser therapy, 5 required additional cryotherapy and 1 eye was given adjuvant intravitreal melphalan. 4 eyes underwent secondary enucleation. All eyes amongst this group received systemic chemotherapy, laser, cryotherapy and 3 eyes received intravitreal melphalan (4 cycles). Kaplan-Meier survival analysis showed an overall globe salvage rate of 93%, 76%, and 65% at 1, 2 and 3 years, respectively. No metastasis or deaths were reported.

Conclusion

Intravenous chemotherapy (IVC) coupled with local therapy remains an effective mode of treatment in select patients with Group D RB despite advancements in treatment modalities like intra-arterial chemotherapy. This is especially promising for developing countries with limited resources and socioeconomic barriers.

Introduction

RB constitutes the most common intraocular malignancy in children, its global incidence being 1 in 18,000 live births [1]. The annual crude incidence of RB in Karachi, Pakistan has been reported to be 4.0/100,000 and 2.4/100,000 in children under the age of 5 and 10 years respectively [2]. RB is curable; however, successful treatment relies on early detection and delayed advancement of disease. The global mean age at presentation for RB was found to be 30.5 months with significant disparity between high
income countries and low to middle income countries, Pakistan belonging to the latter [3]. The increased age of presentation in low to middle income countries likely contributes to the burden of RB in the population as it is more likely to be at a more advanced stage and is thus more challenging to treat [4].

Over time, RB has been staged with various protocols. The ICRB is currently used in Pakistan. It focuses mainly on the extent of tumour seeding in the vitreous cavity and subretinal space with consideration of tumour size and location [5]. Under the ICRB system, eyes are assigned with Groups A to E. Group D eyes are defined as having diffuse vitreous or subretinal seeding and/or massive non-discrete endophytic or exophytic disease which has not yet progressed to Group E [6].

Salvage of eyes is particularly challenging in cases of Group D RB and is often an area of debate and interest for ophthalmologists and paediatric oncologists. Group D sits in between Groups C and E, with Group C being largely treatable and Group E commonly requiring upfront enucleation. Treatment of Group D eyes involves the usage of local consolidative treatments such as laser and cryotherapy along with IVC. This is followed by enucleation if local consolidation fails. Rates of eye salvage in Group D eyes with IVC alone vary from 11 to 47%. Newer modalities such as intra-arterial chemotherapy have been found to salvage 45% of group D eyes [7].

This study aims to present clinical outcomes in patients diagnosed with Group D RB at a tertiary care hospital in Karachi, Pakistan. The data represented may be useful in prediction of eye salvage rates of Group D RB in Pakistan and may be used as an aid in prognosis at tertiary care hospitals in developing countries offering a multidisciplinary approach.

**Material Methods**

This study was a retrospective chart review and data was collected from the Ophthalmology department at Patel Hospital, Karachi between a period spanning nine years. 170 patient files were accessed and assessed with diagnosis of RB. Cases were then categorised according to ICRB staging protocol. All patients diagnosed with intraocular Group D RB in at least one eye confirmed on examination under general anaesthesia (EUA) according to ICRB guidelines were included in the study. Patients with diagnosis of groups A, B, C or E RB without any Group D diagnosis under ICRB classification were excluded. A retrospective analysis was performed to obtain age, age at diagnosis, gender, presenting complaint, laterality of RB, systemic chemotherapy agents used with the number of cycles completed, radiation therapy when applicable, details of local therapy and regression or progression of disease. Complications of treatment offered, metastasis and any deaths were also recorded.

Treatment included IVC in line with the standard vincristine, etoposide and carboplatin protocol which consisted of 6 cycles administered via a central venous line at approximately 28-day intervals. Local treatment involved cryotherapy, administering triple freeze-thaw cycles for each session and laser therapy involving double frequency argon laser. Local treatment was administered at the discretion of the consultant ophthalmologist and the decision to enucleate was determined at multidisciplinary tumour board meetings which included ophthalmologists, paediatric oncologists and radiologists from all over
the country. Presence of high-risk histopathological features post-enucleation prompted the usage of adjuvant chemotherapy. Failure to respond to IVC and local consolidative therapy prompted the usage of intravitreal chemotherapy (IViC) in the form of melphalan.

Data Analysis

All statistical analyses including mean, median and standard deviation were performed by using SPSS version 26. Descriptive statistics were used to summarise the data. Demographic variables were summarised in terms of mean ± standard deviation for quantitative variables. Percentages and frequencies were used to summarise qualitative variables. Survival was estimated and displayed using Kaplan-Meier curves.

Results

Between the period 25th April 2013 to 1st December 2022, 170 patients were referred to the Ophthalmology department at Patel Hospital for RB. Group D RB was diagnosed in 28 patients during EUA. Of these, 22 patients had bilateral disease with Group D in at least one eye, one had bilateral Group D disease whereas six had unilateral Group D disease. Nine patients were excluded from the study because they were examined either for second opinion only or there was loss of follow-up. Therefore, 19 Group D eyes of 19 patients with RB were included in this study. Mean age at diagnosis was 17.2 months. The mean follow-up time for all patients was 57.5 weeks (range 7–263 weeks).

Four Group D eyes were found to have advanced disease and were subsequently referred for primary enucleation. Amongst this group undergoing primary enucleation, in the case of bilateral RB, the contralateral eye was classified as Group E in two patients and Group B in one patient whereas the other had unilateral Group D disease. The Group E eyes were treated with chemotherapy and subsequent enucleation. The normal eye received no treatment but was examined with EUA regularly. The mean age of diagnosis for patients who underwent primary enucleation of the Group D eye was 14.8 months. None of the patients treated with primary enucleation had any recurrences, metastases, or other secondary malignancies.

We attempted to preserve 15 Group D eyes (of 15 patients) with systemic chemoreduction, local consolidative therapy and IViC. Patient parameters are summarised in Table 1. The most common presenting sign was leukocoria (60%), followed by strabismus (20%). Other presenting features including proptosis amounted to 13.33% of the cohort. Amongst the study cohort, bilateral disease was predominant, with 14 (93.33%) bilateral cases whereas unilateral disease was found in one (6.67%) patient. Of the bilateral cases, the majority consisted of Group E in the contralateral eye (85.72%) whereas Groups B and C were reported in one patient each (7.14%). The median age of diagnosis was 32.0 months (mean: 34.7, range: 10.0-72.0). The mean follow-up time was 36.73 ± 16.01 months (range: 17 – 71). A positive family history was found in two patients (13.33%).
Table 1: Patient characteristics on basis of age, gender, presenting sign, classification, and family history

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>N=15 patients</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Male</td>
<td>11</td>
<td>73</td>
</tr>
<tr>
<td>• Female</td>
<td>4</td>
<td>27</td>
</tr>
<tr>
<td>Age at diagnosis (months)</td>
<td>32.0</td>
<td>(34.7, 10.0-72.0)</td>
</tr>
<tr>
<td>Age when first symptoms noticed (months)</td>
<td>Median(mean, range)</td>
<td>18.0(18.1, 8.0-36.0)</td>
</tr>
<tr>
<td>Presenting signs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Leukocoria</td>
<td>9</td>
<td>60</td>
</tr>
<tr>
<td>• Strabismus</td>
<td>3</td>
<td>20</td>
</tr>
<tr>
<td>• Both</td>
<td>1</td>
<td>6.67</td>
</tr>
<tr>
<td>• Other</td>
<td>2</td>
<td>13.33</td>
</tr>
<tr>
<td>Laterality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Unilateral</td>
<td>1</td>
<td>6.67</td>
</tr>
<tr>
<td>• Bilateral</td>
<td>14</td>
<td>93.33</td>
</tr>
<tr>
<td>Classification of contralateral eye in bilateral cases (n=14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• B</td>
<td>1</td>
<td>7.14</td>
</tr>
<tr>
<td>• C</td>
<td>1</td>
<td>7.14</td>
</tr>
<tr>
<td>• E</td>
<td>12</td>
<td>85.72</td>
</tr>
<tr>
<td>Family History</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Present</td>
<td>2</td>
<td>13.33</td>
</tr>
<tr>
<td>• Absent</td>
<td>13</td>
<td>86.67</td>
</tr>
</tbody>
</table>

Overall, chemo-reduction with local consolidation successfully treated 11 of 15 eyes (73.33%). Before and after treatment All eyes received laser therapy whereas five received cryotherapy in addition to laser therapy. One eye was given intravitreal melphalan in addition to local consolidative treatment. Of the eleven eyes that were salvaged, there were no side effects reported. Table 2 shows treatment...
combinations offered. Picture 1 and Picture 2 show fundus photography of the right eye of a patient being successfully treated with IVC and local consolidative therapy.

Kaplan-Meier survival analysis showed an overall globe salvage rate of 93%, 76%, and 65% at one, two and three years, respectively. Figure 1 shows the cumulative eye-survival according to Kaplan-Meier analysis.

Four eyes of four patients were secondarily enucleated. Of the four eyes that underwent secondary enucleation, two (50%) were performed in the first year of follow-up and two (50%) were performed during the third year of follow-up. Indications for secondary enucleation included recurrence of the tumour, extensive retinal detachment, phthisis after local consolidative therapy and presence of resistant, multiple vitreous seeds post-treatment. Three out of these four eyes received four intravitreal melphalan injections each but were found to have either persistent vitreous seeds or exudative retinal detachment on subsequent EUAs. All four enucleated eyes were sent for histopathological assessment and two of them were found to have high-risk histopathological features including optic nerve involvement in one eye and massive choroidal (>3mm) invasion in the other.

Table 2: Treatment combinations offered

<table>
<thead>
<tr>
<th>Total Patients</th>
<th>Treatment Modality</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=19</td>
<td></td>
</tr>
<tr>
<td>Primary Enucleation</td>
<td>4</td>
</tr>
<tr>
<td>Attempted Globe Salvage</td>
<td>15</td>
</tr>
<tr>
<td>Successful Globe Salvage</td>
<td>11</td>
</tr>
<tr>
<td>IVC(VEC) + Laser + Cryotherapy</td>
<td>5</td>
</tr>
<tr>
<td>IVC(VEC) + Laser</td>
<td>5</td>
</tr>
<tr>
<td>IVC(VEC) + Laser + Cryotherapy + IViC (melphalan)</td>
<td>1</td>
</tr>
<tr>
<td>Treatment Failure</td>
<td>4</td>
</tr>
<tr>
<td>N=4</td>
<td></td>
</tr>
<tr>
<td>IVC(VEC) + Laser + Cryotherapy + IViC (melphalan)</td>
<td>3</td>
</tr>
<tr>
<td>IVC(VEC) + Laser + Cryotherapy</td>
<td>1</td>
</tr>
</tbody>
</table>
Discussion

The ICRB defines Group D eyes as having significant tumour burden including large tumours with diffuse subretinal and/or vitreous seeding. Salvage of Group D eyes is particularly challenging with advanced Group D presentation being treated with enucleation [8]. Pakistan contributes a sizeable to the impact of RB in the Asia Pacific region [9] and lacks adequate resources to tackle it. This study looked at the outcomes of being diagnosed with Group D RB at a centre where specialist treatment was available involving a multidisciplinary approach. Specialist treatment for RB is limited in this part of the world and coupled with poor socio-economic factors, leads to a higher mortality rate when compared to the developed world.

The most common presentation in our patients was leukocoria followed by strabismus which are the two most common presenting complaints of RB documented in medical literature [10]. Genetic testing is a scant resource in the developing world, therefore, based on verbal confirmation during history taking, it was found that two patients (13.33%) had a positive family history for RB. This may imply that hereditary RB is not as prevalent in this region when compared to sporadic presentation, this is consistent with the findings of Kalsoom et al. [11].

The mean age of diagnosis in our study was 32 months compared to 21 months in high income countries including the U.K., U.S and France [12], 20 months in Tehran [13] but similar to those reported in India [14]. This increased age of diagnosis is a critical factor in determining patient outcomes. With increased age correlating to an advanced stage of disease, poorer rates of successful treatment and hence higher mortality. This study highlights this, where patients that required enucleation were found to be of an older age compared to the patients with eyes salvaged. Many patients referred to this centre are from rural areas where early detection is near impossible and coupled with financial strains incurred in travelling further deters patients from receiving prompt treatment. This could advocate for the increased age of presentation when compared to our western counterparts. Our results highlight the importance of early diagnosis and the necessity of early referral to specialist centres in Pakistan.

In our study, 14 patients had bilateral intraocular RB with the majority having advanced Group D or E disease. It is worth mentioning that the study cohort majorly comprised of bilateral disease with only one patient with unilateral presentation. However, a study by Supawan et al did not find any significance of pathological risk factors based on gender, and laterality [15].

IVC along with focal therapy remains to be the mainstay of treatment in group D RB eyes [16]. It is widely accepted that despite numerous emerging protocols for Group D eyes, they are still a challenge to treat. The role of laser therapy in treatment of RB is often overlooked and understated despite being an integral part of the treatment regime. Laser is in fact, the most readily available and inexpensive resource available to low income, developing countries [17]. Our success rates using local consolidative therapy raise a question towards the need for a standardised training programme rather than the consultant’s
personal experiences in the treatment of RB. Standardization of laser therapy in line with a protocol may improve its reproducibility in a standard patient cohort. This has previously been discussed by Soliman et al. [18].

We treated a small cohort of 15 Group D eyes with the intention of globe salvage spanning over nine years in which we were able to achieve globe salvage of 11 eyes with IVC coupled with local consolidative therapy. This led to achieving an overall globe salvage rate of 73% which is consistent with the findings of Fabian et al.; a similar study conducted in the U.K. at a larger scale [7]. These findings are also similar to those of Kaliki et al which reported that systemic chemotherapy was the main treatment modality used, giving a globe salvage rate of 58% [19]. Another study by Khaqan et al reported a very comparable globe salvage rate of 72.73% with IVC, laser and/or cryotherapy along with IViC melphalan [20]. In addition to this, a review article by Yet et al also reported the use of systemic chemotherapy with VEC with local consolidative therapy in selected Group D patients and reported salvage rates as high as 87% in China [21]. These comparable studies strengthen the success rates achieved in our study with systemic IVC with local consolidative therapy as a treatment regime for Group D RB.

Out of the four patients that received intravitreal melphalan in adjunct to systemic chemotherapy, three had to undergo secondary enucleation. This is consistent with the findings of Palwasha et al who found no additional benefit with intravitreal melphalan in terms of globe salvage [22]. However, a study by Saima et al reported promising results with intravitreal melphalan in a similar demographic. This difference may be due to a low sample size of patients treated with intravitreal melphalan or the nature of the vitreous seeds. It is reported that vitreous clouds have a better outcome with intravitreal melphalan [23]. In our study, we found that multiple vitreous seeds and those of a large cotton ball appearance are more resistant to intravitreal melphalan. Furthermore, it has been observed that vitreous seeds associated with a non-resolving tumour mass and/or exudative retinal detachment render treatment futile and inevitably result in enucleation [24]. This was also the case in our study where three quarters of the patients treated with intravitreal melphalan were offered secondary enucleation due to associated exudative retinal detachment and non-resolving tumour mass.

There have been various studies on the salvage rates of Group D RB worldwide, but this study is among the few that have been conducted in Pakistan. Discrepancies in reporting of globe salvage rates may occur due to different classification systems used in various studies [25]. Therefore, it is essential to mention the classification used in order to compare findings.

Newer treatment modalities and protocols have increased globe salvage rates, as seen in the developed world where the use of intra-arterial chemotherapy was reported to be superior to IVC [26]. The results of this study show that this progress in increased globe salvage has translated to low income countries as well, given that specialist treatment centres are available.

Limitations
There are several limitations to this study, firstly, patients undergoing primary enucleation were excluded from the study which could imply selection bias. Secondly, visual acuity before or after treatment was not considered, this was partly due to incomplete medical records. Furthermore, the timespan for follow-up is severely truncated due to various factors including incomplete contact information and missed appointments. Also, the study cohort was particularly small in comparison to other studies which hinders the generalisation of these findings. Given the low sample size of our study, it is far from significant in terms of representation of the region. However, the results do show a great deal of promise with an overall globe salvage rate of 72% and no recorded deaths or signs of metastatic spread in the study period. These findings are a step towards better management of the burden of RB in Pakistan.

Conclusion

The results of this study show that IVC coupled with local therapy remains an effective mode of treatment in a select group of patients with Group D RB despite advancements in the field like intra-arterial chemotherapy, especially for developing countries with limited resources and socioeconomic barriers.

Declarations

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Competing Interests

Authors have no relevant financial or non-financial interests to disclose.

Authors Contributions

All authors contributed to the conception and design of the work. Material preparation, data collection and analysis were performed by KMAAJ, AJ and UV. KMAAJ and UV wrote the first draft of the manuscript and all others commented on previous versions of the manuscript. MHC revised the manuscript and produced the final version. All authors read and approved the final manuscript.

Ethics Approval

This is a cross-sectional, observational study. The Ethical Review Committee provided approval for this study.

References


eyes with advanced retinoblastoma at Queen Sirikit National Institute of Child Health: 5 years result. *PloS one, 17*(7), e0270362. https://doi.org/10.1371/journal.pone.0270362


Pictures
Pictures 1 and 2 are available in the Supplementary Files section.

Figures

Figure 1
Kaplan-Meier estimates of globe salvage

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- p1.png
- p2.png