ADVANCED INTRAOCULAR RETINOBLASTOMA

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• No Disclosure
Epidemiology

• The average age-adjusted incidence rate of retinoblastoma in the United States and Europe is 2 to 5 per million children (approximately 1 in 14,000–18,000 live births).

• Incidence is higher (6–10 cases per million children) in Africa, India, and among children of Native American descent in the North American continent.

• Studies from Mexico and Brazil have documented an inverse correlation between the incidence of retinoblastoma and socioeconomic index.
Childhood Cancers Distribution At The Indus Hospital

Childhood Cancer Statistics
(January 2016 – December 2018)
International Classification for Intraocular Retinoblastoma

Fig. 2. International Classification for Intraocular Retinoblastoma. (A) Small tumor confined to the retina and distant from the foveola and the optic nerve (group A). (B1) Two small tumors confined to the retina but adjacent to the optic nerve (group B). (B2) Tumor with small amount of subretinal fluid and no subretinal seeding (group B). (C) Exophytic retinoblastoma with subretinal fluid and seeding (group C). (D) Endophytic retinoblastoma with massive vitreous seeding (group D). (E) Large retinoblastoma filling more than two-thirds of the globe (group E).
Advanced Intraocular Retinoblastoma at Indus Hospital, Karachi (2013-2017)

Total Patients: 57
- Unilateral: 30
- Bilateral: 27

Total Eyes: 84
- A: 2
- B: 19
- C: 5
- D: 12
- E: 41

2/3 (53/79) eyes presented with advanced IO disease
Goals of Treatment

• Save life
• Save vision & globe
• Minimize impact on quality of life
## Multidisciplinary Approach

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General Guideline for Advanced Intraocular Retinoblastoma

- Enucleation
- Conservative Ocular Salvage
  - Chemoreduction with either systemic or ophthalmic artery infusion chemotherapy (IAC) with or without intravitreal chemotherapy
  - Local treatments (cryotherapy, thermotherapy, and plaque radiation therapy)
  - EBRT
Criteria for Upfront Enucleation

- Large tumors filling the vitreous for which there is little or no likelihood of restoring vision
- Neovascular glaucoma
- Opaque media due to hemorrhage
- Pthisis bulbi
- As a salvage treatment in cases of disease progression or recurrence in patients
Enucleation

**PROS**
- To reduce the risk of recurrence /relapse
- Patient may not be requiring any Rx if histopathology is low risk.
- Does not need close monitoring and follow up

**CONS**
- Life long stigma of being enucleated
- High rate of abandonment when advised enucleation
Enucleation; Key Surgical Points

- Minimal manipulation
- Avoid perforation
- Adequate length of optic nerve > 15mm

LEAVING TUMOR BEHIND IN THE OPTIC NERVE POTENTIAL SURGICAL DISASTER IN AN EYE WITH RETINOBLASTOMA
Histology After Enucleation
Histopathological Risk Grouping

• **LOW RISK FEATURES:**
  – Prelaminar invasion/optic nerve head
  – Focal choroidal invasion

• **INTERMEDIATE RISK FEATURES:**
  – Massive choroidal >3mm full thickness
  – Retrolaminar optic nerve invasion
  – Disease in the anterior chamber
  – Intrascleral invasion

• **HIGH RISK FEATURES/ADVERSE HISTOLOGY**
  – Cut end of optic nerve invasion.
  – Transcleral invasion
Post Enucleation Treatment

Enucleation

Histopathology

Low Risk
- No Chemo Therapy

Intermediate Risk
- 4 Cycle of CEV

High Risk
- 2 Cycle of CEV
- Orbital XRT
- 4 Cycles of CEV
Conservative Ocular Salvage

- Systemic chemotherapy
- Focal Treatment (Laser and Cryotherapy)
- Subtenon Chemotherapy
- Intravitreal chemotherapy
- Intra arterial chemotherapy
- Plaque radiation therapy
- EBRT
Systemic Chemotherapy

• To reduce tumor volume (chemoreduction)
• To facilitate the use of local treatments
• To avoid the long-term effects of radiation therapy.
• Continued or initiated with concurrent local control.
• Most regimens include a three-drug combination of vincristine, etoposide, and carboplatin, either alone or alternating with cyclophosphamide and an anthracycline.
• Recently Topotecan has also being used
Focal Therapy
Laser and Cryotheraphy

• These modalities are used in advanced IO retinoblastoma mostly in combination with systemic chemotherapy
• Cryo is used for tumor in the anterior portion of the retina.
• Laser is more commonly used to treat posterior tumor.
• Argon laser in which the laser was applied around the tumor has given way to thermotherapy (diode laser) delivered directly to the tumor surface via infrared wavelengths of light
Subtenon Chemotherapy
(Subconjunctival Chemotherapy)

With the development of new treatments for retinoblastoma, such as intra-arterial and intravitreal delivery of chemotherapy, subtenon chemotherapy is being used less often in the clinical setting.
Intravitreal Chemotherapy

- Intra-vitreal administration of chemotherapy (Melphalan or Topotecan) can control intravitreal seeds.
Intravitreal Chemotherapy
Swiss published experience

- 23 pretreated eyes with active vitreous seeds
- Melphalan 20-30 micrograms every 7-10 days
- Complete response post a median of 4 injections
- Local therapy needed in all except 2
- 17 eyes salvaged

Intravitreal Chemotherapy

• A retrospective study of 264 eyes (250 children) treated with intravitreal melphalan for vitreous seeds over a two-decade period reported a 68% complete remission rate.

• A review showed that extraocular tumor spread, potentially as the result of intravitreal injection, is negligible

• A meta-analysis has shown that significant side effects are uncommon, although each injection results in a small decrease in retinal function, as measured by ERG
Intra-arterial Chemotherapy

• Direct chemotherapy delivery to the tumor via its arterial supply
  – Avoid systemic side effects
  – Increase dose of chemotherapy delivered to the tumor
Intra-arterial Chemotherapy
Historical Background

• Intra-arterial chemotherapy first used in 1950s

• Re-described in Japan in 1993 and 2004
  Mohri M. Keio Igaku 1993; 70: 679-687.

• Further refined in 2008 as super-selective ophthalmic artery infusion (SSOAI)
  Abramson et al. Ophthalmology 2008; 115: 398-404

• Widely promoted as primary treatment to avoid enucleation, as alternative to systemic chemotherapy, or as salvage therapy.
Intra-arterial Chemotherapy

• Prospective, single-arm registry of 95 eyes in 78 patients.
• 2-y ocular EFS 70% for all eyes, 82% for primary and 58% for secondary. 2y ocular EFS 67% for group V eyes, 81% for primary and 52% for secondary.
• 2 metastatic recurrences, 0 deaths.

P Gobin, I Dunkel, B Marr, S Brodie, D Abramson.
Arch Ophthalmol 2011; 129: 732-737

• Retrospective series of 70 eyes in 67 patients.
• For primary treatment, achieved globe salvage in 16/17 (94%) Group D and 5/14 (36%) Group E eyes (ocular EFS not described). For secondary treatment, achieved glove salvage in 62%.
• Ocular complications in 10%, reducing over time. No patients with metastases or death.

C Shields, F Manjandavida, S Lally et al.
Complications of intra-arterial chemotherapy

- Retinal detachment (up to 19.3%)
- Vitreous hemorrhage (18.1%).
- Ptosis (13.6%).
- Dysmotility (6.5%).
- Vascular and ischemic effects (6.2%).
- Optic atrophy (3.4%).
- Phthisis (2.7%).
Intra-arterial chemotherapy plus intravitreal chemotherapy (as needed for vitreous seeding) has improved globe salvage in eyes with advanced retinoblastoma when compared with children who were treated in earlier years with intra-arterial chemotherapy alone.

Intra-arterial chemotherapy plus intravitreal chemotherapy

40 eyes presenting with vitreous seed clouds (class 3 seeds) were retrospectively reviewed in 2 era. In the first era (2011-2016) primary treatment with intra-arterial chemotherapy, while in the later era (2011-2016) simultaneously both intravitreal and intra-arterial chemotherapy.

Children treated in the later era demonstrated shorter time to regression, fewer recurrences, fewer enucleations, and no increased toxicity, including no difference in loss of retinal function by ERG.

Brachytherapy

- Plaque brachytherapy involves placement of a radioactive implant on the sclera corresponding to the base of the tumor to transsclerally irradiate the tumor.
- Iodine 125 and Ruthenium-106 is commonly used.
- It may be used as a primary therapy in large tumor mass
- Recurred tumors after chemo and other focal therapy.
EBRT

• The role of EBRT in advanced intraocular tumor is limited to
  – High risk histology after enucleation
  – Failure of conservative treatment

• Newer methods of delivering EBRT are being applied in an attempt to reduce adverse long-term effects. This includes
  – IMRT
  – Proton-beam radiation therapy

• Preliminary data suggest that proton radiation therapy is associated with a lower risk of radiation-induced malignancy in survivors of heritable retinoblastoma.
Options in Unilateral Advanced Intraocular Tumor

• Enucleation

• Conservative Ocular Salvage
  – Chemoreduction with either systemic or ophthalmic artery infusion chemotherapy (IAC) with or without intravitreal chemotherapy
  – Local treatments (cryotherapy, thermotherapy, and plaque radiation therapy)
  – EBRT
Treatment Options for Bilateral Intraocular Retinoblastoma

• The goal of therapy is ocular and vision preservation and the delay or avoidance of EBRT and enucleation.

• EBRT is now reserved for patients whose eyes do not respond adequately to primary systemic or intra-arterial chemotherapy and local consolidation.

• Tumor burden is usually asymmetric, and treatment is dictated by the most advanced eye.
Factors Determining the Option

• Goals of Treatment
  – Life
  – Prospect of vision
  – Quality of life
• Patient Related
  – Acceptance for enucleation
  – Compliance
  – Finances
• Institution Related
  – Available facilities
  – Expertise
  – Finances
Role of Multidisciplinary Team

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<tr>
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<th>Group 1</th>
<th>Group 2</th>
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<tbody>
<tr>
<td>Median age in Years</td>
<td>2.7</td>
<td>2.4</td>
</tr>
<tr>
<td>M / F ratio</td>
<td>1.6 : 1</td>
<td>1.2 : 1</td>
</tr>
<tr>
<td>Bilateral</td>
<td>42</td>
<td>39</td>
</tr>
<tr>
<td>Unilateral</td>
<td>54</td>
<td>57</td>
</tr>
<tr>
<td>Staging</td>
<td>74%</td>
<td>98%</td>
</tr>
<tr>
<td>Abandonment</td>
<td>48%</td>
<td>30%</td>
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After initiation of multidisciplinary team there has been significant reduction in abandonment, better documentation and protocol compliance resulting in better survival and improvement in rehabilitation of children with Retinoblastoma.

Poster presented in SIOP 2017
Conclusion

- Advanced intraocular retinoblastoma are not uncommon particularly in developing country
- Treatment options include Enucleation and Conservative ocular salvage
- Choice of treatment depends upon many institution and patient related factors
- A multidisciplinary approach is mandatory to get the best result
- Prospective data collection and analysis is way forward
• Acknowledgment
  – Dr Nida Zia
  – Dr Usman
  – Dr Furqan