Update on Retinoblastoma

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Outline

• Introduction
• Genetics
• Presentation
• Classification
• Management
• Challenges in Kenya
Introduction

- Childhood genetic, eye cancer arising from the retina

- Typically occurs before 5 years of age

- 60% unilateral; 40% bilateral; Rarely trilateral

- 10% Family history
Genetics in Retinoblastoma

- RB occurs as a result of RB1 gene mutation
- RB1 gene - tumour suppressor gene

(The Two-Hit Hypothesis)
Germline mutation

• Mutation in all body cells- heritable

• All bilateral, and multifocal, *some unilateral*

• Family history

• RB1 mutation identified in blood

• Risk of second cancers(sarcoma, melanoma, lung)

• Offsprings at risk
Somatic mutation

- Sporadic
- Mutation in retinal cells only
- Non heritable form
- Unilateral and unifocal
- No risk of second cancers
Low Penet trance RB

Unaffected carrier
Mosaicism

• A random mutation in the RB1 gene occurring very soon after conception

• Only some of the child’s body cells will have the mutated RB1 gene

• +/- Develop the disease

• +/- Germ cells involved
MYCN oncogene amplification

• No *RB1* gene mutation

• *RB*\(^{+/-}\) *MYCN*\(^{A}\)

• Aggressive *early onset* RB

• Unilateral

• Neuroblastoma like histology
Presentation

- White reflex 60%
- Strabismus 25%
- Orbital cellulitis
- Ant. segment invasion 1%
- Red painful eye +/- Glaucoma 10%
- Proptosis 50%
IIRC classification

**Group A**
- No visual potential
- Tumor touching lens
- Anterior segment involvement
- Opaque media (hemorrhage)
- Aseptic orbital cellulitis
- Phthisis bulbi

**Group B**
- Glaucoma (neovascular)

**Group C**
- No visual potential

**Group D**
- No visual potential

**Group E**
- No visual potential
- Tumor touching lens
- Anterior segment involvement
- Glaucoma (neovascular)
- Opaque media (hemorrhage)
- Aseptic orbital cellulitis
- Phthisis bulbi
Management

Goals of treatment

• Primary goal: save life
• Secondary goal: salvage eye
• Tertiary goal: salvage vision

Multidisciplinary team approach: ophthalmologist, pathologist, oncologist, radiation oncologist, oculist
Systemic chemotherapy

• First line in salvage therapy group B, C and D
• High risk histopathology post enucleation +/- EBRT
• Prior to enucleation in orbital disease + EBRT
• metastatic RB- Palliative

• Vincristine 1.5 mg/m2(BSA D1) (to a max. of 2mg
• Etoposide 300 mg/m2 BSA D1
• Carboplatin 600 mg/m2 BSA D1
<table>
<thead>
<tr>
<th>Laser photocoagulation 532/810 mm</th>
<th>Cryotherapy</th>
<th>Brachytherapy</th>
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<tbody>
<tr>
<td>Thermotherapy</td>
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<tr>
<td>Ring around the tumour and directly on the tumour</td>
<td>Triple freeze thaw Up to -90 °C directly to the tumour Vascular endothelial damage secondary thrombosis and infarction of the tumour</td>
<td>Basal diameter &lt;16 mm and height &lt; 8 mm Iodine (I 125) and Ruthenium (Ru 106) radioisotopes 40gy over 2-4 days</td>
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<td>Coagulates the vessels Ischaemic tumour damage</td>
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<tr>
<td>Initial treatment for Group A After chemotherapy in group B, C, D</td>
<td>Small Peripheral tumours</td>
<td>Gold plaques sutured onto sclera</td>
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Cryotherapy
Intravitreal chemotherapy

• For persistent/resistant vitreous seeds after systemic chemotherapy

• Melphalan/ Topotecan

• Triple freeze thaw cryotherapy at injection site
Intra-arterial chemotherapy

- Direct treatment of the eye via intra-ophthalmic artery

- Indication: failed systemic chemotherapy and focal therapies

- Caution as first-line treatment for unilateral Groups D and E

- Risk of metastasis in poor follow up
External beam radiation therapy

- Extraocular retinoblastoma in the orbit
- Resistant intraocular RB
- Risk of second malignancies and complications
Vitrectomy?
Enucleation

- All Group E tumours
- Unilateral group C and D
- Failed conservative therapy
- Phthisical eyes after high-dose chemotherapy in orbital disease
- Myoconjunctival technique with orbital implant
- Long optic nerve ≥ 12mm

- Credible histopathology report
Retinoblastoma with extraocular tumour extension

3 to 6 cycles of high-dose chemotherapy

Phthisis bulbi with regressed tumour

Enucleation + non-integrated implant Orbital

Orbital external beam radiotherapy

Persistent extraocular tumour component

Continue until 9 cycles of high dose systemic chemotherapy

Persistent extraocular tumour component

Complete a total of 12 cycles
Genetic testing / counselling and follow up
Patient with RB

Genetic testing

Germline disease → Highrisk follow up

No germline disease → No follow up

No genetic testing

Many family members affected
Bilateral/ multifocal disease → High risk follow up

Unilateral / unifocal disease

Sibling: low risk follow up
Offspring: Highrisk follow up
Follow up

• Salvage therapy: every 3-4 weekly until tumour controlled
• Serial EUAs: 3 monthly up to 2 years
  6 monthly up to 5 years
  Annually or every 2 years for life
• Counselling: other malignancies later, siblings, offspring
• Socket management-cosmesis: orbital implants, conformers, artificial eyes
Challenges

• Late presentation
• Poor Follow up
• Financial challenges
• Limited options e.g no brachytherapy, EBRT
• No readily access to some drugs e.g Melphelan, Topotecan, Cyclosporine
Summary

• Early diagnosis is key for best outcome

• Goal of treatment: Life; Eye; Vision

• Multidisciplinary approach

• Genetic counselling +/- testing mandatory