Retinoblastoma Management: Update

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Retinoblastoma: Background

• Most common primary intraocular tumor in children
• Second only to uveal melanoma as most common primary IO malignancy
• Rare disease: 1/15,000 live births = 350 cases/year in US
• No sex or racial predilection
• New mutations in 90% of cases, family history 10%
• Average age at diagnosis:
  – Average 18 months
  • Bilateral 12 months, Unilateral 24 months
Hey Dr. Berry, How do you treat this?
Presenting Signs

- Presenting signs/symptoms %
  - Leukocoria 56.2
  - Strabismus 23.6
  - Inflammatory Sx 8.9
  - Poor Vision 7.7
  - Family Hx 6.8
  - Routine Exam 2.8

- Rare disease + Leukocoria = Late diagnosis
EVERY 60 SECONDS A CHILD GOES BLIND
Child with newly diagnosed retinoblastoma

<table>
<thead>
<tr>
<th>Is there metastatic disease?</th>
<th>Metastatic disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Intensive multimodal therapy (i.e., high-dose chemotherapy +/- radiotherapy) with autologous stem cell rescue is commonly used; however, this approach remains experimental.</td>
</tr>
<tr>
<td>No</td>
<td>&lt;1%</td>
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Including extra-ocular disease, pinealoblastoma

Is the disease unilateral or bilateral?

<table>
<thead>
<tr>
<th>No</th>
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<tr>
<td>30%</td>
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Including MRI
Is the disease unilateral or bilateral?

- Unilateral
- Bilateral

What is the disease classification?

What is the disease classification in each eye?

EUA
Two important features of RB: Seeding/Calcification

Intraocular calcification:
OCT for diagnosis
What is the disease classification?
INTERNATIONAL CLASSIFICATION SYSTEMS FOR INTRAOCULAR RETINOBLASTOMA

**GROUP A**
Small intraretinal tumors away from foveola and disc
- All tumors are ≤3 mm or smaller in greatest dimension, confined to the retina and
- All tumors are located farther than 3 mm from the foveola and 1.5 mm from the optic disc

**GROUP B**
All remaining discrete tumors confined to the retina
- All other tumors confined to the retina not in Group A
- Tumor-associated subretinal fluid less than 3 mm from the tumor with no subretinal seed

**GROUP C**
Discrete Local disease with minimal subretinal or vitreous seeding
- Tumor(s) are discrete
- Subretinal fluid present or past, without seeding involving up to 1/4 retina
- Local fine vitreous seeding may be present close to discrete tumor
- Local subretinal seeding less than 3 mm (2 DOD) from the tumor

**GROUP D**
Diffuse disease with significant vitreous or subretinal seeding
- Tumor(s) may be massive or diffuse
- Subretinal fluid present or past without seeding, involving up to total retinal detachment
- Diffuse or massive vitreous disease may include “gritty” areas or subretinal tumor mass
- Diffuse subretinal seeding may include subretinal plaques or tumor nodules

**GROUP E**
Presence of any one or more of these poor prognosis features
- Tumor touching the lens
- Tumor anterior to anterior vitreous face involving ciliary body or anterior segment
- Diffuse infiltrating retinoblastoma
- Neovascular glaucoma
- Opaque media from hemorrhage
- Tumor necrosis with opaque orbital calcification
- Phtisis bulbi

A: small and far
B: bigger and/or closer
C: seeding
D: diffuse seeding
E: everywhere
What is the disease classification?

Unilateral

- Group A and B tumors
  - Treatment options include(2):
    - Laser photocoagulation
    - Cryotherapy
    - Plaque radiation therapy

- Group C and D tumors
  - Treatment options include(3):
    - Ophthalmic artery chemosurgery
    - Intravitreal chemotherapy
    - Systemic chemotherapy

- Group E tumors
  - Treatment consists of:
    - Enucleation
    - Adjuvant chemotherapy and radiotherapy for high-risk patients(4)

Age & size of the patient

- Both eyes have disease with a choriocapillaris tumor
  - Treatment options include(2):
    - Laser photocoagulation
    - Cryotherapy
    - Plaque radiation therapy

- Both eyes have disease with a tumor:
  - Treatment options for the second eye include:
    - Ophthalmic artery chemosurgery
    - Intravitreal chemotherapy
    - Systemic chemotherapy
    - Enucleation (group E tumors)(4,5)

- If greater than 1 mm in diameter or have pits (involvement)
  - Both eyes include:
    - Ophthalmic artery chemosurgery
    - Intravitreal chemotherapy
    - Systemic chemotherapy
    - Enucleation (group E tumors)(4,5)
Modern Treatment Options for Intraocular Retinoblastoma:

- Enucleation
- Systemic Chemoreduction
- local chemotherapy: Intra-arterial/intravitreal
- Cryotherapy
- Transpupillary thermotherapy (Argon and Diode Laser)
- Brachytherapy
- External Beam Radiation (rare)

Enucleation

- One hour surgery, curative.
- Curative in 96% of cases
- Advanced Unilateral Cases, Group D or E
- Group E
  - Buphthalmos, NVG, anterior segment or CB invasion, orbital cellulitis, phthisis
Enucleation

  - Tumor recurrence after enucleations 1914-2006
    - 71 pts/1674 pts undergoing enucleation (4.2%)
      - Overall, no downward trend in incidence over time
    - 97% in 12 months
      - Mean 6 months
      - never after 24 months
- bilateral Group E may treat
  - Zhou et al: Risk of masking high risk pathological features if enucleation after 3 months

Chemoreduction

- Carboplatin + Vincristine + Etoposide
  - Bilateral disease: Group B or worse in least affected eye
  - 3 to 6 cycles (months) ** 3 at CHLA for Group B
- Results:
  - 90-100% cure rates for small tumors
  - <50% for Group D
  - Need additional treatment
- Problems:
  - Bone marrow suppression common
  - ? Risk of secondary leukemia
  - Cost/ duration of treatment
Chemoreduction: 6 cycles

- MSKCC (adapted from Japanese technique)
- Infusion of chemotherapy directly into the ophthalmic artery
- Avoids systemic toxicity of drug/achieves higher levels within the globe
- ?local/regional toxicity

Intra-arterial Chemosurgery
Intra-arterial Chemosurgery

- Melphalan, Topotecan, carboplatin
  - Unilateral disease: Group B or worse
  - recurrences
  - 3 cycles (months)
  - 3 months and 6 kilos otherwise bridge therapy

Results:
- >90% cure rates reported for primary therapy in Group D
- >50% for recurrent disease post other therapy
- Need additional treatment
- Technical expertise with interventionalist

Local complications (Transient/Rare)

- Transient
  - Periorbital edema
  - Skin erythema/nasal lash loss
- Rare
  - Avascular retinopathy
  - Sectoral choroidal vascular occlusion
  - Stroke
  - Metastasis
Intra-arterial Chemosurgery

Preliminary arteriogram

1.5 French Magic catheter in origin of left ophthalmic artery prior to infusion

Intra-arterial Chemosurgery: 3 cycles
IA Chemo: Summary

- As primary therapy, IA Chemo probably offers cure rates slightly higher than systemic chemotherapy
  - Higher rate of local side effects
  - Lower rates of bone marrow suppression
  - Toxicity in some cases probably explained by variability in blood flow to ophthalmic territories
- Technique dependent results
- Best candidates:
  - Older than 6 months
  - Primary: unilateral group C,D
  - Salvage: Unilateral retinal and vitreous recurrences

Systemic vs. Intra-arterial

### Table 1. Chemorreduction protocol at CHLA

<table>
<thead>
<tr>
<th>Drug</th>
<th>Standard protocol</th>
<th>First cycle: 50% reduced-dose protocol</th>
<th>Subsequent cycles: 50–100% dose protocola</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>for infants &lt;2 months</td>
<td>for infants &gt;2 months</td>
<td>for infants &gt;2 months</td>
</tr>
<tr>
<td>Carboptin</td>
<td>1.3 mg/kg (390 mg/m²)</td>
<td>6.5 mg/kg (195 mg/m²)</td>
<td>6.5 mg/kg (195 mg/m²)</td>
</tr>
<tr>
<td></td>
<td>1.3 mg/kg (390 mg/m²)</td>
<td>6.5 mg/kg (195 mg/m²)</td>
<td>6.5–13 mg/kg (195–390 mg/m²)</td>
</tr>
<tr>
<td>Etoposide</td>
<td>5 mg/kg (150 mg/m²)</td>
<td>2.5 mg/kg (75 mg/m²)</td>
<td>2.5 mg/kg (75 mg/m²)</td>
</tr>
<tr>
<td></td>
<td>5 mg/kg (150 mg/m²)</td>
<td>2.5 mg/kg (75 mg/m²)</td>
<td>2.5–5 mg/kg (75–150 mg/m²)</td>
</tr>
<tr>
<td>Fluorouracil</td>
<td>0.05 mg/kg (1.5 mg/m²)</td>
<td>not given</td>
<td>0.025 mg/kg (0.75 mg/m²)</td>
</tr>
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</table>

* Patients are increased to 100% if they (1) are ≥3 months of age, (2) show no grade III toxicity to the 75% dose, and (3) have inadequate tumor response to the 75% dose. * Only given to infants >2 months of age.

### Recurrence: Retinal Primary

![Eye Images A and B]
EBR

- Radiation: curative at dose well tolerated by human eye (40-45 Gy)
- Best modality for preserving vision (treats entire eye)
- Side effects:
  - Cataract
  - Bony hypoplasia
  - Second cancers
- Contraindicated in kids <12 months
- Used to be used for seeding
- Best for retinal recurrence in only eye

EBR: Second Cancers

- Risk of second cancer at 50 years:
  - Germinal 36%
  - Somatic 6%
- Sarcomas, brain cancers, melanomas
- Risk greatest for EBR treated germline patients < 12 months of age
Recurrence: Seeding

Seeding Classification

Table 1. Summary of Vitreous Seed Classification and Clinical Findings

<table>
<thead>
<tr>
<th>Class</th>
<th>Type</th>
<th>Description</th>
<th>Regression Characteristics</th>
<th>Median Time to Regression (days)</th>
<th>Median No. of Injections</th>
<th>Median Methylprednisolone Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>Dust</td>
<td>Small granules of vitreous opacities. Can be seen as a vitreous haze overlying tumor.</td>
<td>Typically regress to type 0 (not viable)</td>
<td>2–3</td>
<td>3</td>
<td>20</td>
</tr>
<tr>
<td>Type 2</td>
<td>Spheres</td>
<td>Spherically shaped opacities within vitreous. Dust may be present around spheres. Can be heterogeneously opaque or have a translucent outer shell with relatively transparent or whitish centers.</td>
<td>Initially discrete (pseudogranular) and then disappear, but can become calcific (type I), amorphous (type II), or a mixture of types I and II (type III)</td>
<td>6–7</td>
<td>5</td>
<td>30</td>
</tr>
<tr>
<td>Type 3</td>
<td>Cloud</td>
<td>Dense collection of punctate vitreous opacities. Can appear as a sheet of globules of seed granules and often with a step edge. Dust and spheres are sometimes also visible.</td>
<td>Initially discrete (pseudogranular), become calcific, or disappear, but can remain calcific (type I) or amorphous (type II).</td>
<td>12–14</td>
<td>8</td>
<td>33</td>
</tr>
</tbody>
</table>
Seeding Classification

Figure 1. Illustration summarizing vitreous seed classification and response to intravitreal melphalan: number of injections received, time to response, and mean dose of melphalan per injection.
Vitreous seeding pre-2012

- Unilateral Group B
- After 3 cycles CEV, tumor recurrence noted with vitreous seeding
- Treated with 2 cycles systemic topotecan/cyclophosphamide
- Retinal tumor regressed but the vitreous seeding showed no response

Vitreous seeding pre-2012

- 2 sessions of IAC
  - 5 mg melphalan
  - 8 mg melphalan
- No response by vitreous seeding
- Left eye was enucleated
Intravitreal chemotherapy injection: Munier 2012

- IVC protocol for RB
  - Melphalan 20-30 ug
  - UBM at injection site, 180 degrees away from seeding
  - 32 ga needle
  - Only for isolated vitreous seeding

Intravitreal Melphalan: Injection Technique

- Mark the injection site 3.25-3.5mm posterior the limbus
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• Paracentesis is performed withdrawing 0.1 cc of aqueous humor

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• Paracentesis is performed withdrawing 0.1 cc of aqueous humor
• An injection is done with a 32 G needle in a quadrant of the eye free of tumor
Intravitreal Melphalan: Injection Technique

- Mark the injection site 3.25-3.5mm posterior the limbus
- Paracentesis is performed withdrawing 0.1 cc of aqueous humor
- An injection is done with a 32 G needle in a quadrant of the eye free of tumor
- The needle is visualized behind the lens

- Cryotherapy is applied as the needle is withdrawn
- The eye is then shaken to distribute the chemotherapy
- Surface is bathed in sterile water
Review of IVC complications: Smith SJ BJO 2014

- 10 published studies on IVC for RB
  - 295 patients, 1287 injections, mean F/U 74 months
    - 38 patients with ocular side effects
      - 17 major (2 with RD)
      - 21 minor (IOP, cataract)
    - 1 patient with extraocular spread in Japan
    - 395 injections in 71 patients outside Japan with no extraocular spread

Intravitreal Melphalan: Case 1

- A 2-month-old girl presented to CHLA with bilateral retinoblastoma:
  - OD: Group D
  - OS: Group B
- She was started on systemic chemotherapy with consolidation laser therapy
Intravitreal Melphalan: Case 1

- S/p 4 cycles of chemotherapy and consolidation laser therapy pt had persistent active vitreous seeding OU
- She underwent 2 IVM injections OU (1 week apart) w/ no apparent intra-op or post operative complications

Intravitreal Melphalan: Case 2

- A 6-month-old boy presented to CHLA with unilateral Group D retinoblastoma OD
- He was started on systemic chemotherapy with consolidation laser therapy
Intravitreal Melphalan: Case 1

- S/p 6 cycles of chemotherapy and consolidation laser therapy pt had persistent active vitreous seeding
- He underwent 2 IVM injections OD (1 week apart) w/ no apparent intra-op or post operative complications

Intravitreal Melphalan: Cases 1&2

Case 1

Case 2

1 week s/p 1st IVM injections
Intravitreal Melphalan: Cases 1&2

Case 1

Case 2
Intravitreal Melphalan: Cases 1&2

Case 1

Case 2
Proposed Hypothesis
Proposed hypothesis

Proposed hypothesis
Proposed hypothesis
Intravitreal injections induce a PVD in 24% of adults

Geck et al. Eye 2012
In the phase III ocriplasmin study, PVD could be observed by injecting 0.1 ml of a sham-solution in 10.1 % of control patients.

Stalmans et al. NEJM 2012
Group B eye with diffuse vitreous seeding following systemic chemotherapy

After 6 IVC injections
Local: Cryotherapy for RB

- Best modality for small, peripheral tumors
- Mechanism of action:
  - Cell death through formation of ice ball, apoptosis
- Technique: probe used to indent sclera

Local Therapy: Photocoagulation

- Useful for small (<3mm), posterior tumors
- Options:
  - Argon (photocoagulation)
  - Diode 810 nm (TTT)
Treatment options for RB

- **Enucleation**
  - Unilateral, advanced tumors with poor visual potential
- **Systemic chemotherapy**
  - Small-medium sized tumors, bilateral cases
- **External beam radiation**
  - Systemic chemo failures, older than 12 months
- **Laser/cryotherapy**
  - Small, focal tumors
- **Radioactive plaque**
  - Large focal tumor
- **Intra-arterial chemotherapy infusion**
  - Large tumors with seeding (EBR contraindicated)
Retinoblastoma Summary

• Rare tumor
• Improving prognosis for eye salvage
• Various treatment modalities depending on the Age of patient and laterality of disease
• As well as size/location/extent of seeding of the tumor
• Local therapies are becoming common
Thank you!