Diagnosis and Management of Neuroblastoma

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University of Michigan Medical Center
Neuroblastoma: A puzzling disease

- **Signs and Symptoms:** Variable.
- **Biology:** Variable.
- **Staging:** New.
- **Response Grading:** Good luck
- **Therapy?** Depends on type.
- **CIBMTR Forms?** Good luck.
Q.12. Is subsequent HCT planned. In COG = Yes.
Q31. Donor: Autologous (99%). Never cord. Rarely allo (1%)
Q42. Product type: PBSC. Never marrow.
Q72. Was product manipulated pre-infusion: No
Most common: a) Thiotepa- Cyclophosphamide  
b) Carboplatin-Etoposide-Melphalan  
c) Busulfan-Melphalan  
ATG: No, Irradiation with HCT: No
Q346. Is additional therapy planned.  
Q.353. Local radiotherapy: Yes  
Q.356: Immunotherapy: Yes (Dinutuximab)
CIBMTR Form 2450: Neuroblastoma

• **Q7.** Did pt receive a 2\textsuperscript{nd} HCT.  Yes (Planned)
• **Q16.** Graft failure: I’ve never seen it happen
• **Q19-33:** Not relevant. No GVHD in auto-HCT
• **Q39.** Liver prophylaxis: Typically is Ursodiol.
• **Q46.** VOD / SOS: Defined using CTCv5.0
• **Q75-92.** Assessment. (Common answers)
  - **Q79.** By Molecular Tests: No  
  - **Q82.** By Flow Cytometry: No
  - **Q85.** By Cytogenetics: Sometimes
  - **Q92.** By Radiology: Yes
  - **Q95.** By Clinical / Heme: Yes
Neuroblastoma: We know so much.

One of a handful of tumors with a specific marker: Urine catecholamines (VMA, HVA).

One of first tumors with its own tumor specific scan: MIBG scans

One of the first tumors to use “maturation agents” Cis retinoic acid (Accutane).

We often can do so little. Historically, one of the least treatable malignancies in the pediatric population.
Neuroblastoma: Basics

- 2nd most common solid tumor in children.
- 1 per 7000 births. **Only 750 new cases per year in US.**
- Average age at diagnosis = 22 months. 95% of cases are < 10 yrs

Abdominal mass: neuroblastoma
Portrait of a Tumor

Patterns of Classification

Clinical
- Age, Stage

Radiological
- MIBG scans

Biological
- MYCN, Alk mutations

Histology
Diagnosing NBL: Look in 3 places

- **Bones**
  - MIBG scan

- **Bone Marrow**
  - BM biopsy

- **Tissue / Nodes**
  - CT / MRI
  - Biopsy
Diagnosing NBL: Surgical Biopsy

Biopsy: Small round blue cell tumor

Bone marrow Clusters of cells (rosettes)
Round Blue Cell Tumors: Four types

- Neuroblastoma
- Ewings sarcoma
- Rhabdomyosarcoma
- Non-Hodgkin's Lymphoma
Neuroblastoma: Terms are confusing

• It’s a spectrum.

Normal Nerve

Ganglio-neuroblastoma

Neuroblastoma

Typically retains some nerve structure, with fibrillary material and axons, but abnormal.

Typically: highly undifferentiated. Little background fibrillary material or axonal structure.
Neuroblastoma: Terms are confusing

- It’s a spectrum.

Typically,
- Low stage
- Younger (< 18 mo)

Typically:
- Higher stage
- Older (>18 mo)
Diagnosing NBL: CT / MRI

Normal CT scan of abdomen
Radiographic Signs: Neuroblastoma
• Aorta pushed forward
• Calcifications inside the mass
• Kidney is pushed down.
Diagnosing NBL: Urine catecholamines

**Measure VMA and HVA**
- Spot collection, not 24-hour.
- Levels are age dependent.
- Normal ~ < 10-15 mg/gm creat

**What does all this even mean?**
Diagnosis: Urine catecholamines

Measure the end-products: VMA and HVA

Excreted in the urine.
Diagnosis: Urine catecholamines

Measure the end-products: VMA and HVA
Diagnosis: Urine catecholamines

Measure the end-products: VMA and HVA
Thus, where does Neuroblastoma arise?

• **Neuroblastoma arises in cells that make epinephrine (Epi) and norepinephrine (NE).**

• Thus, NBL arises in cells along the spinal cord (called ganglia) that transmit nerve impulses, or in the adrenal gland.
Neuroblastoma: Tumor Cytogenetics
What does MYCN amplification mean

**Normally:** we have 2 copies of MYCN on chromosome 2p

**Amplified:** > 2 copies are present

1<sup>st</sup> reported 1980’s (Look, Seeger)

**Associated with:**
- Aggressive Disease.
- Inferior survival
- Treat as High risk (any stage)
Neuroblastoma: Tumor Cytogenetics

- **MYCN**: Amplified in 30% of high stage disease
  All other stages: present in < 10%.
  Treat as high risk if present.

- **ALK mutations**: Seen in 8% of all NBL.
  Risk of Familial NBL and ALK
  Therapy: Add ALK inhibitors

- **Gain of 17q**: Most common. Seen in 70% of NBL

- **Ploidy (DNA content)**: Hyperdiploid is favorable.
Diagnosing NBL: MIBG scans

Required Evaluation:

• Surgical Biopsy.
• Bilateral Marrow Bx
• CT / MRI
• Urine catecholamines
• MIBG scans
MIBG: Background

MIBG: Meta-IodoBenzylGuanidine
Developed at University of Michigan (1979)
Structurally similar to norepinephrine.

MIBG imaging: Began in 1983.
90% of neuroblastoma are MIBG avid.

Historically: For relapsed / refractory disease.
Current focus: Move MIBG into frontline therapy
(COG ANBL1531)
Neuroblastoma: Clinical signs

• **How do children present:**
  Limping, Not walking: Bone involvement. **Painful.**
  Pallor, Fatigue: Anemia, Thrombocytopenia.

• **Look at the eyes:**

  ![Raccoon’s eyes: Periorbital Bruising](image)
  ![Horner’s syndrome: Triad Ptosis, Anhidrosis, Meiosis.](image)
Spectrum of Behavior: Age dependent

**Infants / Toddlers (0-18m):**
- 30% of cases.
- Less aggressive.
- Prognosis > 85%.
- Lower stage (Stage 1-2-3, 4s).
- Arise from neural crest cells that hadn’t fully matured.
- Spontaneous regression common.

**Age > 18 months:**
- 70% of cases.
- Very aggressive.
- Prognosis < 50%.
- Majority present with metastases.
- Arise from cells that have mutated.

Prognosis declines with age
Case presentation: 4 year old male

- Left adrenal mass on MRI. MIBG avid in one spot.

- Biopsy performed. Do NOT attempt resection at Dx.
- Bone marrow was negative.
- Tumor biology: MYCN amplified.

What stage is the patient?
What stage is the patient?

Depends upon what staging system we use. We have a new staging system: INRG

International Neuroblastoma Risk Group
INRG Staging

INSS system: Old system. NOT used any longer.
Staged patients 1 – 4.
Staging was surgically dependent.

INRG: New system. Based on CT/MRI
Image Dependent Risk Stratification (IDRF)
New Stages: L1, L2, M and MS (Not Stage 1-4)
Staging is not based upon skill of the surgeon.

THIS IS OUR NEW STAGING SYSTEM
## INRG Staging: Comparison to INSS

<table>
<thead>
<tr>
<th>INSS (OLD)</th>
<th>INRG (NEW)</th>
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<tbody>
<tr>
<td><strong>Stage 1:</strong> Localized. Complete resection</td>
<td><strong>Stage L1:</strong> Localized tumor</td>
</tr>
<tr>
<td><strong>Stage 2:</strong> Localized, incomplete resection</td>
<td>On CT / MRI:</td>
</tr>
<tr>
<td>2a. Regional nodes negative</td>
<td>• Confined to 1 body compartment.</td>
</tr>
<tr>
<td>2b. Regional nodes abnormal</td>
<td>• Does not involve vital structures.</td>
</tr>
<tr>
<td><strong>Stage 3:</strong> Unresectable. Crosses midline.</td>
<td><strong>Stage L2:</strong> Local-Regional Tumor.</td>
</tr>
<tr>
<td><strong>Stage 4:</strong> Metastatic disease</td>
<td>• Tumor encasing vessels.</td>
</tr>
<tr>
<td><strong>Stage 4S:</strong> Infants &lt; 1 year.</td>
<td>• Tumor infiltrating adjacent organs.</td>
</tr>
<tr>
<td>• Localized tumor</td>
<td>• Tumor invading neuroforamen.</td>
</tr>
<tr>
<td>• Stage 1 or 2, with skin, liver or BM</td>
<td>• Involves 2 contiguous body regions.</td>
</tr>
<tr>
<td>• BM &lt; 10%. No bone disease.</td>
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### Cohn, JCO 2009
Does the patient even qualify as having high risk disease?

4 year old, L2 disease, MYCN amplified
High Risk Candidates: EFS < 50%

INRG: S. Cohn, JCO 2009
International Data Base
COG, SIOPEN, German, Japan
Total = 8800 neuroblastoma

Overall n=8800
EFS 63%
OS 70%

Stage 1, 2, 3, 4S (L1, L2, MS)
EFS 83%, OS 91%

Stage 4 (M)
EFS 35%, OS 42%

Ganglioneuroblastoma
EFS 97%
OS 98%

Neuroblastoma
EFS 83%
OS 90%

MYCN non-amplified
EFS 87%
OS 93%

MYCN Amplified
(any stage NBL)
EFS 46%, OS 53%
“High Risk” is Also Age Dependent

Patients $\geq 18$ months in age:

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<thead>
<tr>
<th>Stage</th>
<th>Age</th>
<th>MYCN</th>
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<tr>
<td>L2</td>
<td>$&gt; 18$ months</td>
<td>Amplified</td>
</tr>
<tr>
<td>M</td>
<td>$&gt; 18$ months</td>
<td>Any</td>
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Patients $< 18$ months in age:

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<td>Amplified</td>
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Therapy is based upon risk

Low Risk
- Surgery vs Observation

Interm Risk
- Chemo
- Surgery

High Risk
- Chemo
- Surgery
- HCT
- XRT
- Ab

Induction → Consolidation → Maint.
Current therapy for high risk neuroblastoma

Therapy is built upon 30+ years clinical trials.

1980’s:
- Chemo #1
- Chemo #2
- Stem Cell Harvest
- Chemo #3
- Chemo #4
- Chemo #5
- Surgery
- Chemo +

1990’s:
- BMT
- Local Radiation

2000’s:
- Accutane
- + Immuno-therapy

Current Transplant Techniques
- Single Transplants
- Tandem Transplants
Neuroblastoma: Historical Perspective

Major Transplant Trials in North America

- **CCG-321-P**
  - Can BMT be done?
  - Best donor?
  - Allo vs Auto

- **CCG-3891**
  - Is BMT even useful?
  - BMT vs Continued Chemotherapy

- **COG-A3973**
  - Stem cells?
  - Role of “purging” stem cells?

- **COG ANBL0532**
  - Are 2 BMT better than 1?
  - Yes.

**Autologous**

**BMT superior**

Yes to stem cells.
No to Purging.

Marrow as donor source

1980 1990 2000 2010
Neuroblastoma: Historical Perspective

Major Transplant Trials in North America

- CCG-321-P: Can BMT be done? Best donor? Allo vs Auto
- CCG-3891: Is BMT even useful? BMT vs Continued Chemotherapy
- COG-A3973: Stem cells? Role of “purging” stem cells?
- COG ANBL0532: Are 2 BMT better than 1?

ALK gene abnormalities

Immuno-therapy (Dinutuximab)

First North American BMT trial for NBL.

<table>
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<th>Transplant type</th>
<th>4 year Disease Free Survival</th>
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<tr>
<td>Autologous</td>
<td>45%</td>
</tr>
<tr>
<td>Allogeneic</td>
<td>25%</td>
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- Established role for autologous transplants in NBL.
- Sibling donor only.
- Bone marrow as stem cell source.
- Transplanted at end of induction therapy.

Matthay, JCO 1994
Neuroblastoma: Historical Perspective

Major Transplant Trials in North America

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- Stem cells?
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COG ANBL0532
- Are 2 BMT better than 1?

- After Induction: Patients randomized to either:
  - Transplant or 3 more cycles of induction chemo.
- One of the largest COG Neuroblastoma trials to date.

Matthay, NEJM 1999

![Graph showing event-free survival rates over years after first randomization.](attachment:graph.png)

- BMT arm: 34% 3-yr EFS
- Chemo arm: 22% 3-yr EFS
Neuroblastoma: Historical Perspective

Major Transplant Trials in North America

- **CCG-321-P**: Can BMT be done? Best donor? Allo vs Auto
- **CCG-3891**: Is BMT even useful? BMT vs Continued Chemotherapy
- **COG-A3973**: Stem cells? Role of “purging” stem cells?
- **COG ANBL0532**: Are 2 BMT better than 1?

Timeline:
- 1980
- 1990
- 2000
- 2010
COG A3973 (2001-2006)

- First major test of Stem Cells in Neuroblastoma Therapy.
- Stem Cells collected after 2 cycles chemo. Given after 5.
- “Purging” process done in lab to remove possible tumor.

![Tumor free survival graph](image)

- **unpurged (n=245)**
  - 2 yr EFS = 49 +/- 3%

- **purged (n=244)**
  - 2 yr EFS = 47 +/- 3%

**p = 0.7881**

Kreissman.
Neuroblastoma: Historical Perspective

Major Transplant Trials in North America

- CCG-321-P
  - Can BMT be done?
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  - Allo vs Auto

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  - Stem cells?
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- COG ANBL0532
  - Are 2 BMT better than 1?
Tandem BMT: COG ANBL0532

Park J, JAMA 2019

- Stem cells collected after cycle 2.

- Induction
  - Topotecan-Cytoxan

- BMT #1 (CEM)
  - Cytoxan-Thiotepa

- BMT #2 (CEM)

Graph showing event-free survival over years after randomization, with log-rank P = .006.
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<tr>
<th></th>
<th>Single HCT</th>
<th>Tandem</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td>3-yr EFS</td>
<td>48%</td>
<td>62%</td>
<td>0.006</td>
</tr>
<tr>
<td>3-yr OS</td>
<td>69%</td>
<td>74%</td>
<td>0.25</td>
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</table>
Current COG NBL Study: ANBL1531

Arm A & B: Tandem BMT. ± MIBG
Arm C: MIBG. Single BMT.
Arm D: MIBG non-avid (10%)
Arm E: ALK mutation (10%)

Given thru Induction., starting with cycle 2. Held during apheresis and HCT. Restarted x 1–year post-HCT.

Arm E
Crizotinib
ALK+

Arm A
Arm C
Cycle 1
Cycle 2
Harvest
Cycle 3

Tandem BMT
Tandem BMT

MIBG
MIBG

Cycle 4-5
Cycle 4-5

Tandem BMT
BuMel

Cycle 4-5
Cycle 4-5

All arms get radiation and immunotherapy post-BMT
“The red circles are your red blood cells. The white circles are your white blood cells. The brown circles are donuts. We need to talk.”