Neuroblastoma

Meaghan Granger, MD
Cook Children’s Medical Center

Objectives

- Review diagnosis, pathophysiology, and unique paraneoplastic syndromes associated with neuroblastoma
- Review the international staging criteria and prognostic indicators for all stages of NBL and the biologic differences that correlate with age and outcome.
- Discuss treatment of neuroblastoma
- Discuss the challenges of treatment in patients with relapsed or refractory neuroblastoma
Neuroblastoma facts

- Neural Crest Origin
  - Ganglioneuroma
  - Ganglioneuroblastoma
  - Neuroblastoma
- Sympathetic Chain Ganglion
- Most common solid tumor (not CNS)
- Comprises 8 to 10% pediatric cancer
- 500 cases per year
- Toddlers most affected—mean age 2 years
- Extremely variable clinical outcome

Neuroblastoma diagnosis
**Neuroblastoma sites of disease**

<table>
<thead>
<tr>
<th>Site</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdomen</td>
<td>50%</td>
</tr>
<tr>
<td>Paraspinous</td>
<td>24%</td>
</tr>
<tr>
<td>Chest</td>
<td>20%</td>
</tr>
<tr>
<td>Neck</td>
<td>4%</td>
</tr>
<tr>
<td>Pelvis</td>
<td>2%</td>
</tr>
</tbody>
</table>

**Abdominal Mass**

- Differential includes Wilms tumor, hepatoblastoma, and germ cell tumor
- Symptomatic or asymptomatic
- Systemic symptoms with weight loss, diarrhea, fever
- Hepatomegaly
- Adrenal origin

**Spinal Cord Compression**

- Oncologic emergency
- Back pain
- Neurologic deficits
- Bladder dysfunction or UTI
- Neurologic recovery depends on level
- Treatment is decompression by chemotherapy, surgery or radiation
**Horner syndrome**
- Clinical triad
  - Ptosis
  - Miosis (constricted)
  - Anhidrosis
- Compression of sympathetic nerve ganglia at any level
- Facial, jaw, or chest mass

**Pelvic Mass**
- Constipation
- Urinary retention
- Renal failure due to compression of the kidneys

**Skin Involvement**
- "Blueberry Muffin"
- Scalp Nodule
- Most often seen in 4S Neuroblastoma
Racoon Eyes

- Metastases at skull base, sphenoid and temporal bones
- Palpebral vessel obstruction
- Tumor tissue in orbits (arrows)

NEJM, 2003: 349, e4

Limp/Bone Pain

- Refusal to walk
- Leg pain severe, recurrent
- Often presents as toxic synovitis with a bone scan or MRI showing disease

Paraneoplastic Syndromes

1. Excessive catecholamine secretion: flushing, sweating, palpitation, headaches, and hypertension
2. VIP secretion: intractable watery diarrhea from secretion of hormone from neuroblastoma cells
3. Acute myoclonic encephalopathy or opsoclonus/myoclonus syndrome
Opsoclonus/Myoclonus Syndrome

- “Dancing-eyes, dancing-feet”
- Most children less than 2 years
- Of patients with OMS only half associated with NBL
- Often low stage NBL
- Autoantibodies bind to cerebellar and peripheral nerves
- Disease remission doesn’t guarantee neurologic remission
- Immunologic treatment with steroids, IVIG, and/or rituxan as part of clinical trial

Disease Evaluation

- International Neuroblastoma Staging System (INSS) Tests
- Primary tumor imaging
  - CT/MRI and MIBG (if available)
- Metastatic evaluation
  - Bone marrow evaluation - aspirate and biopsy
  - Bone Scan and MIBG
  - Lymph node evaluation - clinical
  - Abdominal evaluation with CT or MRI
  - Chest evaluation with CT, CXR
Evaluations

- Large abdominal mass
- Bone scan showing RUQ mass
- Calcified mass plain film
- Mediastinal mass
- MIBG lesions pre and post treatment

MIBG Scan

- Nuclear medicine scan or "Neuroblastoma Scan"
- MIBG (metaiodobenzylguanine) is an analog of a catecholamine precursor and expressed on neuroblastic tumors
- Most neuroblastomas are MIBG-avid (10% not)
- MIBG may also be used therapeutically as part of clinical trials

**MIBG Scan Image**: 123I-MIBG image of 10-mo-old child with posterior mediastinal primary tumor, widespread bone marrow involvement, and bulky metastatic deposits in right parietal skull and left sphenoid/orbit. No MYCN amplification and therefore prognosis is favorable.
Diagnosis

- Pathologic tissue showing neuroblastoma
- Bone marrow + elevated catecholamines (urine VMA/HVA are markers of biologically active tumors)

International Neuroblastoma Staging System (INSS)

- Stage 1: Excised localized tumor, negative nodes
- Stage 2a: Localized tumor with incomplete resection, negative nodes
- Stage 2b: Localized tumor with or without complete resection, ipsilateral nodes positive
- Stage 3: Unresectable unilateral tumor crossing midline, or localized unilateral tumor with contralateral nodes
- Stage 4: Disseminated disease except for 4S
- Stage 4s: Localized primary tumor not crossing midline with disseminated disease limited to skin, liver, and/or bone marrow in child <1 year age
Pathologic Classification

- Histologic Classification (FH vs. UF) Shimada classification
  - Schwannian stroma
  - Degree of tumor maturation
  - Mitotic/Karyorrhexis index (high is UF)
  - Patient age (older is UF)

N-MYC

- Amplified proto-oncogene in 20% tumors is associated with
  - Advanced stage
  - Rapid progression
  - High levels of expression
  - Usually not seen in infants

Neuroblastoma in the Making

Nature Reviews Cancer
Prognostic factors

GOOD
- Localized disease
- Age < 18 months (formerly 365 days)
- Favorable histology
- Single N-myc copy
- Hyperdiploidy
- No abnormalities of chromosome 1p, 11q or 17q
- High trkA expression (marker of differentiation)

BAD
- Advanced stage
- Age > 18 months
- Unfavorable histology
- MYCN amplification
- Diploidy
- 1p deletion and/or 17q gain
- 11q LOH
- Low trkA expression
- High LDH, ferritin, NSE
- Urine VMA/HVA elevated

COG Risk Group Determination

- INSS Stage
- Age at diagnosis
- Histology
- MYCN copy number
- Tumor Ploidy

<table>
<thead>
<tr>
<th>INSS Stage</th>
<th>Age</th>
<th>MYCN status</th>
<th>chroma</th>
<th>DNA index</th>
<th>Risk group</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0-14 years</td>
<td>Any</td>
<td>Any</td>
<td>Any</td>
<td>Low</td>
</tr>
<tr>
<td>1A/1B</td>
<td>&lt;365 days</td>
<td>Any</td>
<td>Any</td>
<td>Any</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>&gt;365 days-21 years</td>
<td>Normal</td>
<td>Any</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;365 days-21 years</td>
<td>Amplified</td>
<td>Favorable</td>
<td>Line</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>&lt;365 days</td>
<td>Normal</td>
<td>Any</td>
<td>Any</td>
<td>Intermediate</td>
</tr>
<tr>
<td></td>
<td>&gt;365 days-21 years</td>
<td>Amplified</td>
<td>Unfavorable</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>&lt;365 days</td>
<td>Normal</td>
<td>Any</td>
<td>Any</td>
<td>Intermediate</td>
</tr>
<tr>
<td></td>
<td>&gt;365 days-21 years</td>
<td>Normal</td>
<td>Favorable</td>
<td>Line</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;365 days-21 years</td>
<td>Normal</td>
<td>Unfavorable</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>&lt;365 days</td>
<td>Normal</td>
<td>Any</td>
<td>Any</td>
<td>Intermediate</td>
</tr>
<tr>
<td></td>
<td>&gt;365 days-21 years</td>
<td>Any</td>
<td>Any</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>&lt;365 days</td>
<td>Normal</td>
<td>Favorable</td>
<td>Any</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>&gt;365 days-21 years</td>
<td>Normal</td>
<td>Any</td>
<td>Intermediate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;365 days-21 years</td>
<td>Amplified</td>
<td>Unfavorable</td>
<td>Any</td>
<td>Intermediate</td>
</tr>
</tbody>
</table>

INSS, International Neuroblastoma Staging System
COG Risk Groups

- High: 42%
- Low: 39%
- Itmd: 19%

Survival According to COG Risk Group

Neuroblastoma Treatment

Goal: Tailor therapy according to patient risk group
Low Risk Neuroblastoma

- Current study for patients with perinatal study observes infants with localized neuroblastoma
  - Age less than 3 months
  - Disease limited to adrenal gland
  - Small mass: <16mm

Intermediate Risk Neuroblastoma
**Intermediate-Risk Neuroblastoma Study**
- Reduction of therapy only for patients biologically favorable tumors (without LOH 1p36 and 11q23)
- Chemotherapy cycles 2, 4, or 8
- Maintain OS of >95% for all patients

**High Risk Neuroblastoma**
- Most common form of disease is advanced
- Survival is 40% at best
- Initial good response to therapy
- Achieving a complete response to induction therapy impacts long-term survival
- Multi-phasic therapy
- High incidence of recurrent disease
- Emergence of resistant tumor cells is challenge
High Risk Therapy

- Induction aimed at controlling disease and achieving a complete response
- Surgery most often necessary to achieve CR
- Consolidation uses intensive chemotherapy to overcome chemotherapy resistance to residual disease using autologous stem cell rescue
- Radiation is given to enhance local control at primary tumor site and residual bone sites
- Maintenance phase continues therapy with cis-RA and biologic therapy

Stem Cell Transplant in Neuroblastoma

- Randomized trial (CCG-3891) first showed a significant improvement in EFS using ABMT
- Preparative regimen gives intensive chemo aimed at chemotherapy resistant cells and "rescues" body with autologous stem cells
- Peripheral blood stem cells can be used safely
- Manipulations of stem cells
  - CD34+ selection
  - G3973 showed no benefit to stem cell purging
- Harvested stem cells are evaluated for tumor cell contamination prior to infusion and must be less than 1/100,000

Stem Cell impact on EFS in Neuroblastoma
Retinoic Acid Therapy

- Down regulates N myc
- Active with minimal residual of disease
- Pulse therapy for 2 of 4 weeks
- Treatment in maintenance for 6 months to 1 year
- Waxy capsules containing oil based liquid
- Accutane now prescribed only by iPledge system

Retinoic Acid in CCG-3891

Combining cis-retinoic acid and ABMT on EFS
Future Challenges

GOAL: To develop more effective treatment for patients with HIGH risk disease

- OLD “Dirty bomb” tactic – Intensive therapy
  - Prohibitive toxicity
  - Resistant tumor cells not eliminated
- NEW “Smart bomb” tactics – Biologically based agents combined with chemotherapy, surgery, radiation

Neuroblastoma Relapse

- Relapse is biggest problem in HIGH risk neuroblastoma
- Disease becomes resistant to therapy
- Chances for survival very diminished
- Salvage therapy can induce remission in some cases
  - Institutional protocols
  - COG clinical trials
  - NANT clinical trials
Mechanisms of Targeted Therapy in NBL

- Differentiation Therapy
- Immunotherapy
- Tumor Targeting
- Metabolic Pathways
- Cytotoxic Agents

Fenretinide

- Vitamin A analog
- 4-HPR
- Induces apoptosis by unclear mechanisms (increased ceramide levels, NFκb, PKC…)
- Independent of other retinoid receptor pathways
- Minimal hematopoietic toxicity
- Decreased night vision
- Current NANT trials oral lipid suspension and IV form

Mechanisms of Targeted Therapy in NBL

- Differentiation Therapy
- Immunotherapy
- Tumor Targeting
- Metabolic Pathways
- Cytotoxic Agents
GOAL: Mobilize host defenses to kill tumor cells

- monoclonal antibodies target the disialoganglioside GD2 (highly expressed on neuroblastoma)
- mediate tumor-cell kill by leukocytes and complement
- has been effective against refractory neuroblastoma in bone marrow
- Several trials currently underway

Anti GD-2 Immunotherapy

- GD2 expressed on 98% Neuroblastoma
- Non-cross resistant with chemotherapy
- Mechanism of Action mediated by NK and T cells
- 10-15% responses in previous Phase I and II studies for relapsed patients
- Current randomized trial ongoing in maintenance
  - Hu14.18 + Il-2 + GMCSF and cis RA
  - cis RA alone

Immunotherapy principles
Mechanisms of Targeted Therapy in NBL

- Differentiation Therapy
- Immunotherapy
- Tumor Targeting
- Metabolic Pathways
- Cytotoxic Agents

MIBG therapy: Phase I

- Matthay K., JCO, 1998; 16, 229-36
- 30 patients with refractory neuroblastoma
- I−--MIBG from 3-18 mCi/kg
- Hematologic toxicity – dose level
  18mCi/kg required stem cell support
- Minimal hematopoietic toxicity
- Response rate 37%
- Approximately 10% patients non-MIBG avid
MIBG setup

MIBG therapy

MIBG therapy: Phase II

- 104 patients
  - Prior stem cell transplant
  - Soft tissue, bone, and marrow involvement
- 28% required stem cell support
- 45% response rate (CR+ PR)
- Correlation of dosimetry with toxicity and response
- Correlation of marrow involvement with delayed platelet recovery
MIBG Response

NANT 9901
- I131-MIBG + CEM + PBSC
  - Day -21: MIBG
  - Day -7 to -4: Carboplatin, Etoposide, Melphalan
  - Day -3 to -1: Rest
  - Day 0: PBSC infusion

Mechanisms of Targeted Therapy in NBL
- Differentiation Therapy
- Immunotherapy
- Tumor Targeting
- Metabolic Pathways
- Cytotoxic Agents
**CEP-701**

- Tyrosine kinases Trk A, B, and C important in developing and maintaining nervous system
- Trk A and C expression is favorable
- Trk B expression is unfavorable and correlates w/ Nmyc expression
- CEP-701 inhibits all Trk with anti-angiogenic and apoptotic effects
- Oral agent with high bioavailability

**Mechanisms of Targeted Therapy in NBL**

- Differentiation Therapy
- Immunotherapy
- Tumor Targeting
- Metabolic Pathways
- Cytotoxic Agents

**ABT-751**

- Novel oral antimitotic agent
- Binds to colchicine site on B-tubulin
- Currently in Phase II study
- Active in adult and pediatric cancers
Mechanisms of Targeted Therapy in NBL

- Differentiation Therapy
- Immunotherapy
- Tumor Targeting
- Metabolic Pathways
- Cytotoxic Agents
- Genetic Pathways

Candidate Drugs

- Bortezomib
- SAHA
- BSO
- Aurora kinase inhibitors
- mTOR inhibitors
- Tumor vaccine
- Zometa
- Alk inhibitors
- Bevacicumab
- Valproic acid

There is hope
Keep Breathing