Neuroblastoma – MIBG Imaging and MIBG Therapy Update

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Neuroblastoma

• The most common extracranial solid tumor of childhood
• Accounts for 8% of all childhood cancers
• Heterogeneous disease with wide range of clinical behavior
• Arises from neural crest derived sympathetic nervous system precursor cells
• Median age at diagnosis 15 months
Neuroblastoma: Mets at diagnosis

- 50% of infants and 2/3 of children 1 year and older
- 20% of patients refractory to induction chemotherapy
- 40% will relapse despite complete/partial remission
- Metastasizes most commonly to
  - cortical bone and bone marrow
  - regional and distant LN’s
  - liver
## Staging

### INSS (1988, REVISED 1993-POSTSURGICAL STAGING)

- **1-** Localized tumor complete gross resection no LN’s
- **2-** Localized tumor with incomplete resection and/or ipsilateral LN’s
- **3-** Unresectable crosses midline or contralateral LN’s
- **4-** distant metastases
- **4s-** < 12 months with mets to liver, skin, bone marrow only

### INRGSS (2009-PRESURGICAL STAGING)

- **L1-** localized tumor to one body compartment w/o vital structures involved
- **L2-** local/regional tumor 2 body compartments or encasing vessels/invading organs/extending into spinal canal
- **M-** distant metastases
- **MS-** <18 months with mets to liver, skin, bone marrow only

*J Clin Oncol 2009; 27(2):298-303*
Staging: Image Defined Risk Factors

• Terminology
  – Encasing
  – Invading
  – Compressing

• Anatomic Regions:
  – Neck, thorax, abdomen/pelvis

• Adjacent structures:
  – Aorta/branches
  – IVC/veins
  – Liver, kidneys, trachea, diaphragm, etc.
Staging

• Biological markers:
  – MYCN oncogene amplification
  – Tumor differentiation
  – Mitotic activity- Mitotic Karyorrhexis Index (MKI)
  – DNA index (ploidy)
  – +/-Segmental chromosomal aberrations
COG Risk Group Determination

- INSS/INRG Stage
- Age at diagnosis
- Histology
- Biology/Genetics

- Determines intensity of therapy
- Developed from over 20 years of clinical trials
- Unlike many other cancers, stage 4 ≠ high risk
Prognosis

- **Low-risk group**: 5-year survival rate that is higher than 95%.
- **Intermediate-risk group**: 5-year survival rate is around 90% to 95%.
- **High-risk group**: 5-year survival rate around 40% to 50%.

London W.B. COG Statistics and Data Center 1986-2001 (n=2,621)
Diagnostic imaging
Diagnosis-Imaging

- Anatomic imaging (CT and MRI)
- I-123 MIBG
- 99m-Tc bone scan
- FDG PET
I-123/I-131 MIBG

- MIBG chemically related to norepinephrine
- Type I catecholamine reuptake system which is overexpressed in neuroendocrine tumors
- 90% neuroblastoma is MIBG-avid
- MIBG first used as an antihypertensive agent in 1987 at U of Michigan
- When labeled with I-123 or I-131, MIBG has both diagnostic and therapeutic utility in neuroblastoma and other neuroendocrine tumors
MIBG-normal distribution

- Myocardium
- Liver
- Bowel
- Salivary glands
- Olfactory mucosa
- Normal adrenal

- Renal excretion/bladder
- Low level uptake in the lungs at 24 hours
- Focal uptake in atelectasis or pneumonia
- Brown adipose tissue—most frequently neck/supraclavicular
MIBG-Curie scoring

- The Curie score can define patient outcome and is a more reliable/consistent method to score response to therapy.

- 10 segments (1 soft tissue)
- Each segment scored 0-3.
- Summate scores. Max = 30
- Skeletal score (per segment)
  - 1 = 1 distinct lesion
  - 2 = 2 distinct lesions
  - 3 = ≥ 50% of a segment.
- Soft tissue scoring
  - 1 = 1 MIBG avid ST lesion
  - 2 = > 1 MIBG avid ST lesion
  - 3 = occupies ≥ 50% region (chest or abd-pelvis)
Curie Scoring

Curie score and outcomes

(A) EFS by Curie score (≤2 vs. >2) after induction (P < 0.001), based on Youden index determination of optimal cut-point. (B) EFS by Curie score (0 vs. >0) after induction (P = 0.003), for patients with MYCN-amplified tumors.

MIBG v bone scan

• MIBG False positives uncommon
  – Sensitivity: 88-93%
  – Specificity: close to 100%

• SPECT-CT increases diagnostic certainty

• 99m-Tc-MDP bone scan
  – Sensitivity: 70-78%
  – Specificity: 51%
Conclusions:
- MIBG is significantly more sensitive for individual lesion detection in relapsed NB than FDG-PET.
- FDG-PET can play a complementary role, particularly in soft tissue lesions.
- Complete FDG response did not always correlate to MIBG response.
Role of MIBG in Neuroblastoma Therapy

- **Salvage therapy**
  - Single agent
  - Tandem MIBG
- **Palliative therapy**
- **18 mCi/kg** OFTEN requires ASCT
- **12 mCi/kg** if no stem cells
- **First line**
  - Single agent
  - Combined therapy regimen

Phase II Study on the Effect of Disease Sites, Age, and Prior Therapy on Response to Iodine-131-Metaiodobenzylguanidine Therapy in Refractory Neuroblastoma

*Katherine K. Matthay, et al.*
*Janet Veatch, et al.*
Toxicity

• Early:
  – Rarely- nausea and vomiting in the first 2 days
  – Myelosuppression typically 4-6 weeks after
  – Rarely- decrease renal function (concomitant chemorx)
  – Rare- hypertensive crisis

• Late:
  – Hypothyroidism
  – Persistent myelosuppression
  – Induction of secondary cancers
8 year old female diagnosed in February 2011. Curie score of 3 at end of induction; up and down course with relapses.
Post therapy #1: 234 mCi

6 wk post #1: 2 mCi
Post Therapy Scan

• The last thing that happens before the patient leaves the hospital
• Take advantage of the large dose to see full extent of disease
• Patterns of uptake uniquely seen:
  – Central brain and cerebellum
  – Normal adrenal gland
  – Thyroid (despite blockade)
  – Spleen
  – Lung
2 y 9 mo
291 mCi
• Increased conspicuity of lesions on the post therapy scan
• Uptake in the spinal cord is not typically seen and should raise suspicion for CNS disease
Improving MIBG Therapy

- Tandem MIBG based on response of first tx
- MIBG as component of myeloablative therapy
- MIBG combination therapy
  - Agents known to upregulate norepinephrine transporter
- MIBG to newly diagnosed neuroblastoma
High-Risk NBL Treatment - Current off study

Standard

Induction

Consolidation = ASCT

Maintenance (ANBL0032)

Harvest enough Stem cells for 4 bags 2 ASCT

Cycle 1

Cycle 2

Cycle 3

Cycle 4

Cycle 5

Cycle 6

Surgery

Focal radiation to primary tumor bed

TC: Thiotepa Cytoxan
CEM: Carbo, etoposide, melphalan
BuMel: Busulfan Melphalan

BIOTHERAPY CH14:18 /IL-2/GMCSF + Isotretinoin

Children’s Healthcare of Atlanta | Emory University
ANBL1531—Phase 3 study of MIBG (or crizotinib) added to standard therapy for patients with HR NB

2 X 2 Factorial Design – assess potential for interaction
Adaptive design: “Non-inferiority” question: 1) Tandem + MIBG vs Tandem alone, 2) Tandem + MIBG vs BuMEL + MIBG
Summary

• Imaging plays an important role in staging of neuroblastoma
• MIBG is the core functional agent used to stage neuroblastoma and monitor therapy response
• MIBG therapy is promising for MIBG-avid disease
• MIBG is better than bone scan, if available
• FDG PET may be helpful in patients with MIBG non-avid disease
References:


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