I-131 MIBG for Therapy of Neuroblastoma

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Functional Imaging of Neuroblastoma

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Neuroblastoma

- 7.2% of cancers in children < 15 y/o in US
- Most common extracranial solid tumor of childhood
- ~ 650 new cases per year in US
Diagnosis of Neuroblastoma

- Unequivocal pathologic diagnosis from tumor tissue based on light microscopy
  
  OR

- Bone marrow aspirate or biopsy with unequivocal tumor cells AND increased urine or serum catecholamine metabolites
Clinical Presentation of Neuroblastoma

- Abdominal distention
- Bone pain
- Incidental
- Occasional
  - Opsomyoclonus-ataxia (dancing eyes)
  - Horner’s syndrome
    - Ptosis – drooping eye lid
    - Myosis - contraction of the pupil
    - Endophthalmos – sunken in globe
  - Treatment resistant diarrhea (VIP production)
  - Hypertension
    - Renal artery compression
    - Catecholamines
Where is the Primary Tumor

- Anywhere along the sympathetic paravertebral chain
  - Adrenal medulla ~50%
  - Abdomen including adrenal ~80%
  - Chest ~15%
  - Neck, other, undetected ~5%

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Where Does It Metastasize

• Bone
• Bone Marrow
• Lymph Nodes
Tracer pathophysiology

- hNET uptake
  - mIBG
  - HED
  - EPI

- Glucose metabolism
  - FDG

- Somatostatin receptor

A positron emitting tracer of hNET is inherently better than the single photon agent mIBG.
Approaches to Imaging of Neuroblastoma

- **Less specific functional imaging agents (not nonspecific)**
  - Glucose metabolism
  - Bone turnover
  - Amino acid uptake and protein synthesis
  - DNA synthesis
  - Membrane synthesis
  - Membrane permeability
  - Blood flow
  - Hypoxia
Fig. 1. A diagrammatic representation of the topology of the human norepinephrine transporter (hNET) protein. Indicated are the positions of the amino acids which are mutated in the naturally occurring hNET variants and examined in this study. From: Runkel: Pharmacogenetics, Volume 10(5). July 2000. 397-405.
hNET

- member of the Na+- and Cl--dependent family of neurotransmitter transporters
- highly homologous to other members of this family, such as
  - serotonin transporter (SERT)
  - dopamine transporter (DAT)
- 617 amino acids with 12 transmembrane domains
  - cytoplasmatic NH2 and COOH termini
- hNET gene on long arm of chromosome 16
Function of hNET

- Responsible for the rapid reuptake of the neurotransmitter norepinephrine into the presynaptic nerve terminals
- Leads to the rapid termination of neurotransmission
MIBG (meta-iodobenzylguanidine)

- Developed by Wieland and colleagues at University of Michigan late 1970s for imaging the adrenal medulla
- Pheochromocytoma localization reported by Sisson - NEJM 1981
- Neuroblastoma localization reported by Treuner - Lancet 1984

[Chemical structure of MIBG and Norepinephrine]
Donald M. Wieland, Ph.D.

meta-iodobenzylguanidine (MIBG)

[¹¹C]meta-hydroxyephedrine (HED)

[¹¹C]epinephrine (EPI)
# Properties of Radionuclides That May Be Used To Label MIBG And Its Analogs

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>Mode of Decay</th>
<th>T 1/2</th>
<th>Principal Photon Energy</th>
<th>Principal Particulate Emissions</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{123}$I</td>
<td>Gamma, EC&lt;sup&gt;a&lt;/sup&gt;</td>
<td>13.2h</td>
<td>159 KeV</td>
<td>Low energy Auger elections</td>
<td>Near ideal gamma camera imaging agent; various accelerator routes of production; supply and cost remain problems. Permits SPECT.</td>
</tr>
<tr>
<td>$^{125}$I</td>
<td>Gamma, EC&lt;sup&gt;a&lt;/sup&gt;</td>
<td>60d</td>
<td>35KeV</td>
<td>Multiple low energy Auger electrons</td>
<td>Widely used for animal and in vitro studies. May have utility for the therapy of micrometastases and intra-operative tumor location with probe detectors.</td>
</tr>
<tr>
<td>$^{131}$I</td>
<td>Gamma, β&lt;sup&gt;-&lt;/sup&gt;</td>
<td>8.05d</td>
<td>364(637)&lt;sup&gt;b&lt;/sup&gt;(723)&lt;sup&gt;b&lt;/sup&gt; KeV</td>
<td>Multiple β&lt;sup&gt;-&lt;/sup&gt; (69-190KeV)</td>
<td>Less than optimal for gamma camera imaging. Suitable for therapy of larger tumor deposits. Convenient compromise agent, approved by FDA.</td>
</tr>
<tr>
<td>$^{18}$F</td>
<td>β&lt;sup&gt;+&lt;/sup&gt;</td>
<td>110m</td>
<td>511&lt;sup&gt;c&lt;/sup&gt; KeV</td>
<td>β&lt;sup&gt;+&lt;/sup&gt;</td>
<td>Label for MFBG and FIBG.</td>
</tr>
<tr>
<td>$^{11}$C</td>
<td>β&lt;sup&gt;+&lt;/sup&gt;</td>
<td>20m</td>
<td>511&lt;sup&gt;c&lt;/sup&gt; KeV</td>
<td>β&lt;sup&gt;+&lt;/sup&gt;</td>
<td>Label for HED and epinephrine.</td>
</tr>
<tr>
<td>$^{76}$Br</td>
<td>β&lt;sup&gt;+&lt;/sup&gt;</td>
<td>16.2h</td>
<td>511&lt;sup&gt;c&lt;/sup&gt; KeV</td>
<td>β&lt;sup&gt;+&lt;/sup&gt;</td>
<td>Label for MBrBG which has been used for PET of cardiac autonomic innervation.</td>
</tr>
<tr>
<td>$^{211}$At</td>
<td>α</td>
<td>7.2h</td>
<td>77-92&lt;sup&gt;d&lt;/sup&gt; KeV</td>
<td>α</td>
<td>Label for MABG which has potential for α therapy.</td>
</tr>
</tbody>
</table>

EC<sup>a</sup> = electron capture  
β<sup>b</sup> = minor but still significant emission  
β<sup>c</sup> = Annihilation photon  
α = Annihilation photon  
γ = Gamma rays from α decay  
MIBG = Meta-iodobenzylguanidine  
MBrBG = Meta-bromobenzylguanidine  
FIBG = Fluoro-iodobenzylguanidine  
MABG = Meta-astatobenzylguanidine  
HED = Hydroxyephedrine  

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I-131 mIBG study of a 2 y/o with newly diagnosed neuroblastoma

it is possible to obtain high quality images with I-131 mIBG
I-131 mIBG study of a 2 y/o with newly diagnosed neuroblastoma
9 year old boy with recurrent neuroblastoma
9 y/o boy with recurrent neuroblastoma - MIBG
$^{123}$I-MIBG Scintigraphy and [$^{18}$F]FDG PET CT in Neuroblastoma

Susan E. Sharp MD, Barry L. Shulkin MD, Wayne L. Furman MD, & Michael J. Gelfand MD
mIBG SPECT
mIBG SPECT CT: Zvi Bar-Sever
In use for over 20 years
Is there a role?
What is it?
The Plan

• Up Front
• Multiple Infusions
• Tandem doses
• Low doses
131I-MIBG as a First Line Treatment in Advanced Neuroblastoma

- Hoefnagel CA, ...QJNM 1995; 61-64
• 31 children ages 7 months to 13 years
• 10 stage III, 21 stage IV
• At least 2 cycles of 131I-MIBG therapy followed by evaluation of resectability
  – 100 to 200 mCi
  – Then 100 mCi at 4 week intervals
  • 6 patients (2 cycles)
  • 12 (3)
  • 6 (4)
  • 3 (5)
  • 4 (6)
Responses to 131I-MIBG up front therapy

- Volume of primary tumor: 73% objective response
  - 1 CR
  - 21 PR
  - 8 SD

- Metastatic disease (21 stage 4): 81% objective response
  - 2 CR
  - 15 PR
  - 4 SD
Responses to 131I-MIBG up front therapy

• General condition improved dramatically
• In most patients pain disappeared within days of first treatment
• Surgical excision n=16 (of 31)
  – Complete resection 3
  – at least 95% resection in 12
• 3 patients minimal residual disease did not have surgery
• 3 partial resection (75-95%)
• 4 stable disease but inoperable
Responses to 131I-MIBG up front therapy

- 12 patients died 3-29 months after 131I-MIBG therapy
  - 9 recurrent NB
  - 3 complications of treatment (hemorrhage post op, BMT)
Results

• Objective response to MIBG (>70%) higher than response to MIBG after conventional therapy (35%)

• Toxicity lower upfront
  – Side effects of chemotherapy do not occur
    • Nausea, vomiting, alopecia, cytopenia, infection, hemorrhage, weight loss
CONCLUSIONS

• Upfront 131I-MIBG therapy feasible
• Effectiveness in attaining operability of primary tumor at least equals that of chemotherapy
  – Less toxicity
Tumor Response and Toxicity with Multiple Infusions of High Dose 131I-MIBG for Refractory Neuroblastoma

Methods

• Retrospective review of 28 patients with relapsed, refractory neuroblastoma treated with multiple infusions of MIBG
  – March 1986 to April 2003
  – UCSF, CHOP

• Phase 1 and phase 2 trials
  – NBL
  – Age 1-40
  – Failure to achieve CR or PR with standard therapy or PD at any time
  – Normal baseline organ function
RESULTS

• 28 patients – 62 infusions
• All patients heavily pretreated
• Median interval between treatments ~ 100 days
RESULTS

• 14 patients had significant response to the first infusion (CR/VGPR/PR)
• 8 patients had significant response to the second infusion
RESULTS

• Overall disease improvement:
  – 11 (39%)
  – 2 MR (mixed response)
  – 6 SD
  – 9 PD

• Toxicity
  – 13 became plt dependent
  – 15 transfusion dependent
RESULTS

- Survival
  - 10 alive 5-51 months after treatment
  - 17 died of progressive disease, 1 AML, 1 bronchiolitis obliterans organizing pneumonia

- Overall response 39%
$^{131}$I-MIBG Double Infusion with ASCT for Neuroblastoma: A NANT Study

Rationale for Double MIBG

- $^{131}$I-MIBG can provide radiotherapy targeting both primary and metastatic tumors
- Response rate to single doses of $^{131}$I-MIBG is 30-40% in refractory neuroblastoma
- Activity of $^{131}$I-MIBG infused has been limited by radiation safety and by myelosuppression
- Widely spaced MIBG treatments (8-12 weeks) waiting for hematopoietic recovery may allow tumor to regrow
Hypothesis

Further anti-tumor activity may be achieved with a rapid sequence double infusion of $^{131}$I-MIBG, supported by autologous stem cell transplant.
N2000-01 Schema

Day 0  14  28  56

$^{131}$I-MIBG  PBSC  Evaluation

K.K. Matthay
## N00-01: MIBG Double Infusion Dose Escalation

<table>
<thead>
<tr>
<th>Level</th>
<th>Cumulative RMI (cGy)</th>
<th>$^{131}$I-MIBG (mCi/kg) #1, #2</th>
<th>Cumulative $^{131}$I-MIBG (mCi/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1</td>
<td>400</td>
<td>12, X</td>
<td>≅ 24</td>
</tr>
<tr>
<td>Level 2</td>
<td>600</td>
<td>15, X</td>
<td>≅ 30</td>
</tr>
<tr>
<td>Level 3</td>
<td>800</td>
<td>18, X</td>
<td>≅ 36</td>
</tr>
<tr>
<td>Level 4</td>
<td>800</td>
<td>21, X</td>
<td>≤42</td>
</tr>
</tbody>
</table>

K.K. Matthay
### Average Red Marrow Index (RMI) and mCi/kg $^{131}$I-MIBG

<table>
<thead>
<tr>
<th>Level</th>
<th>RMI cGy</th>
<th>Range</th>
<th>MIBG mCi/kg</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (n=3)</td>
<td>425</td>
<td>320-505</td>
<td>23</td>
<td>22-25</td>
</tr>
<tr>
<td>2 (n=6)</td>
<td>522</td>
<td>377-592</td>
<td>30</td>
<td>24-33</td>
</tr>
<tr>
<td>3 (n=3)</td>
<td>602</td>
<td>572-657</td>
<td>46</td>
<td>40-50</td>
</tr>
<tr>
<td>4 (n=7)</td>
<td>642</td>
<td>487-892</td>
<td>41</td>
<td>33-43</td>
</tr>
</tbody>
</table>
Response to Double MIBG

Pre-therapy
7/21/04

Post-therapy
10/05/04

K.K. Matthay
**Outcome after Double MIBG**

- Responses (20 evaluable)
  - 1 PR
  - 8 MR
  - 5 SD
  - 6 PD

- Median FU all pts is 386 days (57-696)
- 8 patients died of PD at 85-483 days
- 1 with PR died 14 months later with toxicity after other therapies
- 12 patients alive median 107 days (57-696)
Double $^{131}$I-MIBG with ASCT

Conclusions

- Administered activity of $^{131}$I-MIBG can be safely doubled with this approach to 36-49 mCi/kg
- The relative RMI is lower with the second dose
- Thrombocytopenia is the main toxicity of double MIBG, abrogated by ASCT
- Non-hematologic toxicity minimal
- The responses suggest anti-tumor effect in a highly refractory population
- Future strategies include addition of radio-sensitizing or synergistic agents with the $^{131}$I-MIBG

K.K. Matthay
mIBG - Current Administered Dose

Curative - 2.0 mCi/kg to max 200 mCi.  
(initially 5.0 to max 300 mCi)

Active palliative - 1.5 mCi/kg to max 150 mCi.  
(initially 2.0 to max 200 mCi)

Palliative (Pediatrics) - 0.5 mCi/kg to max 20 mCi.

Alexander J.B. McEwan
Two Strategies for Radioisotope Therapy ($^{131}$ImIBG)

• “Big Bang”
  - High unit dose
  - Toxicity rescue
  - Single treatment
  - Possibly precludes further treatments
  - High complexity
  - Always in patient

• “Steady State”
  - Low unit dose
  - High cumulative dose
  - Multiple treatments
  - Titrate to toxicity
  - Low complexity
  - Usually outpatient

Alexander J.B. McEwan
<table>
<thead>
<tr>
<th>Treatment Plan</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction Rx</td>
<td>3 - 4 therapies at 10 - 12 week intervals</td>
</tr>
<tr>
<td>Maintenance Rx</td>
<td>If a response is seen at induction, then 50% of induction dose at approx 16 week intervals extending to 6 - 9 monthly continued for as long as a response is seen</td>
</tr>
<tr>
<td>Palliative Rx</td>
<td>Low dose treatment at 4 - 8 weekly intervals as OP to control symptoms</td>
</tr>
</tbody>
</table>

Alexander J.B. McEwan
Palliative Low Dose mIBG Therapy in Neuroblastoma

- 0.5 mCi/kg to maximum 25 mCi
- Administered every ~ 4 - 6 weeks
- Observe post injection for ± 30 minutes
- Post therapy imaging at 24 - 72 hours
- Continue until efficacy is not seen
Low Dose mIBG Therapy

- 8 patients with advanced disease
- Pain is major symptom
- Treated with 0.5 mCi/kg to maximum of 25 mCi
- Pain relief in 7/8
- Often occurs within 24 hours
- Persists from 4 - 6 weeks
- Moderate - severe thrombocytopenia acceptable

Alexander J.B. McEwan
Stable disease is common
Response is inversely proportional to tumor burden.
Palliative responses are very common
There appears to be a cumulative dose response
Tolerance probably has not been reached.
Treatments may continue “indefinitely” as maintenance
Response may be sustained for several years
Toxicity is acceptable at the doses administered and should not reduce therapy goals
Probable survival benefit
Probable progression free interval

Alexander J.B. McEwan
CONCLUSIONS

- I-131 MIBG therapy has limited efficacy in the treatment of neuroblastoma
  - Up front
  - Pre BMT
  - Double dose
  - Multiple smaller doses
- Ultimate role not yet determined
- Efforts to increase uptake via hNET expression may help
THANKS

- Sandy McEwan MD
- Kate Matthay MD