I\textsuperscript{131}-MIBG Therapy for Neuroblastoma

Meaghan Granger, MD
August 14, 2012
Objectives

- What is MIBG?
- Review Neuroblastoma as a context for MIBG and challenges of relapsed/refractory disease
- Discuss radiotherapy for cancer
- Review response rates with MIBG trials in past and discuss future directions
What is $^{131}$-MIBG?

$^{131}$-MIBG is taken up in 90% of neuroendocrine tumors and is sensitive and specific for

*imaging*

and

*therapy*
What is $^{131}$-MIBG?

- MIBG (meta-iodobenzylguanaine) is an analogue of norepinephrine that is concentrated in sympathetic nervous tissue and taken up into tumor tissue.
- $^{131}$-MIBG is MIBG with a radiation-containing Iodine molecule added.
4 year old?

Neuroblastoma
- Abdominal mass
- NMYC amplified
- Incomplete response to therapy
- Transplant
- Radiation
- Surgery
- Salvage chemotherapy
- I131-MIBG
- Antibody therapy
Neuroblastoma: Context for $^{131}$-MIBG

- Neural Crest Origin
  - Ganglioneuroma
  - Ganglioneuroblastoma
  - Neuroblastoma
  - Pheochromocytoma
  - Paraganglioma
- Sympathetic Chain Ganglion
- Most common solid tumor (not CNS)
- Comprises 8 to 10% pediatric cancer, 15% of deaths
- 500-700 cases per year
- Toddlers most affected—mean age 2 years
- Extremely variable clinical outcome
COG Risk Group Determination

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

HIGH
INTERMEDIATE
LOW
WE’VE GOT YOUR SIZE IN FRIES!

Enjoy our World Famous Fries™ in Small, Medium and NEW LARGE size. Great with a meal or as a snack, McDonald’s® french fries are made from specially selected Russett potatoes and served up hot, crisp and golden delicious. So c’mon...reach for the fun. Go for the big taste of NEW LARGE size fries today!
Survival According to COG Risk Group

The good news and the bad news
Relapse is biggest problem in HIGH risk neuroblastoma

Refractory disease to induction in 20-30%

Disease becomes resistant to therapy
Chances for survival very diminished, 10% OS
Many cases can become “chronic” disease
Salvage therapy with new agents can induce remission in some cases
Similar to norepinephrine (catecholamine)

90% of neuroblastoma produce catecholamines

90% of neuroblastoma detected by MIBG scans

MIBG therapy:

Began in 1987 at U of Michigan

Developed as antihypertensive therapy

Now diagnostic and therapeutic for NBL/neuroendocrine

MIBG therapy: Background

MIBG

Courtesy G. Yanik 2008
- Uptake-1 is found in normal tissues
- Uptake-1 also overexpressed in neuroendocrine tumors
- Substrate for the norepinephrine transporter
- Norepinephrine uptake is responsible for MIBG uptake in neuroendocrine tumors
Radiation - Biologic Effect

- Local DNA damage
- Quantity of damage
- Accumulation of damage leads to loss of control over cellular functions
- Loss of control can yield apoptosis
What about the Radiation part?
What is Radiation?

Radiation is the release of energy in the form of particles/waves

Alpha, beta, and gamma

α
β
γ

Paper  Aluminium  Lead
Gamma Rays?
Patient Radiation Exposure

Whole Body Dosimetry

*Body uptake of radioactivity*

$I^{131}$- MIBG targeted dose = 18 mCi / kg of
Measured by serial “counts” at a constant distance from patient
Median whole body dose 292,000 mrem ~2cGy
Critical organs: liver, bladder, spleen, marrow, and salivary glands
Stem Cell support at doses >12 mCi/kg

Tumor Dosimetry

*Tumor Uptake by radioactivity*

Measured by MIBG scan post therapy
MIBG Therapy Outline

Day 0
MIBG Infusion
2 hour infusion

Day 1 to 4
Radiation Isolation

Day 7
Tumor Dosimetry
(Measure tumor uptake)

Pre-therapy scan

Parental visitation restricted for 72 – 96 hours

Post therapy scan
Iobenguane (mIBG) I 131 Therapy Procedure
**I¹³¹-MIBG Therapy Procedure**

- MIBG travels through bloodstream
- Uptake into NBL cells
- Excess eliminated through urine/fluids
- Foley catheter for continuous removal
Role of MIBG

• Salvage therapy
  ➢ Single Agent
  ➢ Tandem MIBG

• Palliative therapy

• First line
  ➢ Single Agent
  ➢ Combined
MIBG THERAPY IN ADVANCED NEUROBLASTOMA
MIBG EARLY PHASE TRIALS
## MIBG early phase trials

<table>
<thead>
<tr>
<th>No. Patients</th>
<th>MIBG Dose</th>
<th>Response</th>
<th>Complete Response</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>50/220 mCi</td>
<td>0</td>
<td>0</td>
<td>1991</td>
</tr>
<tr>
<td>25</td>
<td>1-2.5Gy</td>
<td>33%</td>
<td>0</td>
<td>1990</td>
</tr>
<tr>
<td>30</td>
<td>2.6-18.2 mCi/kg</td>
<td>37%</td>
<td>1</td>
<td>1990</td>
</tr>
<tr>
<td>Phase II</td>
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<td></td>
</tr>
<tr>
<td>53</td>
<td>100-200 mCi</td>
<td>56%</td>
<td>7</td>
<td>1991</td>
</tr>
<tr>
<td>164</td>
<td>18 mCi/kg</td>
<td>36%</td>
<td>13</td>
<td>2007</td>
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<tr>
<td></td>
<td>(12 if no stem cells)</td>
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Phase II MIBG (18 mCi/kg)

Grade 3 or 4 Toxicity in 164 patients

- Low blood counts
  - 33% PBSC support (ANC<200 X 2 wks)
  - 70% platelet support (PLT<20K)
- Secondary MDS/AML in 4 patients 2%
- Pulmonary (pneumonia; effusion) 4%
- Hepatic (elevated lab tests) 5%
- Fever with Neutropenia 10%
- Infection 11%
- Hypothyroidism 6%
Patient with Measurable Disease - response of PR Rx with 18 mCi/kg

Pre-therapy

Post therapy
MIBG: Overall survival
47% at 1 yr and 31% at 2 yr.

Matthay et al, J Clin Oncol, March 2007
Phase II MIBG (18 mCi/kg)

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If we look closer at this group of patients
Phase II MIBG (18 mCi/kg)

<table>
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<th>Criteria</th>
<th>Response</th>
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<tbody>
<tr>
<td>SD &gt; 2 mos</td>
<td>37%</td>
</tr>
<tr>
<td>CR + PR</td>
<td>37%</td>
</tr>
<tr>
<td>Bone/BM</td>
<td>45%</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>50%</td>
</tr>
<tr>
<td>B/BM + soft tissue</td>
<td>26%</td>
</tr>
<tr>
<td>Prior ASCT</td>
<td>26%</td>
</tr>
<tr>
<td>No Prior ASCT</td>
<td>25%</td>
</tr>
</tbody>
</table>

n=164
Improving MIBG?

1. Tandem MIBG in rapid sequence
2. MIBG as component of MAT
3. MIBG combination therapy
4. MIBG to newly diagnosed neuroblastoma
TANDEM MIBG
## Tandem MIBG NANT-2000-01

<table>
<thead>
<tr>
<th>DAY</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>(^{131}\text{I-MIBG #1})</td>
</tr>
<tr>
<td>14</td>
<td>(^{131}\text{I-MIBG #2})</td>
</tr>
<tr>
<td>28</td>
<td>ASCT</td>
</tr>
</tbody>
</table>
Response to Tandem MIBG

Pre-Therapy
Day -4

Post-Therapy
Day +56
Conclusions of Tandem MIBG

- Tandem MIBG with PBSC is tolerable and effective
- Median red marrow dose at Level 3 is 577 cGy
- The recommended level for future studies is Level 3: 18 mCi/kg x 2
- The best efficacy is against bone and soft tissue lesions, with an apparent lower response in bone marrow
- This regimen may be more effective by combination with an agent targeting bone marrow disease

Matthay et al., J Clin Oncol 2009
MIBG + MAT
MIBG Combined with MAT (CEM)

<table>
<thead>
<tr>
<th>Day</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day -21</td>
<td>$^{131}$I-MIBG</td>
</tr>
<tr>
<td>Day -7</td>
<td>Carboplatin, Etoposide, Melphalan</td>
</tr>
<tr>
<td>Day -6</td>
<td>Carboplatin, Etoposide, Melphalan</td>
</tr>
<tr>
<td>Day -5</td>
<td>Carboplatin, Etoposide, Melphalan</td>
</tr>
<tr>
<td>Day -4</td>
<td>Carboplatin, Etoposide</td>
</tr>
<tr>
<td>Day –3 to -1</td>
<td>REST</td>
</tr>
<tr>
<td>Day 0</td>
<td>Hematopoietic Stem Cells</td>
</tr>
</tbody>
</table>

Dose escalation 12, 15, 18 mCi $^{131}$I-MIBG
MIBG Combined with CEM

Phase I Response (CR+PR) 22% in refractory patients

Phase II Response  (CR + PR) 16%
   (CR + PR + minor) 40%

Matthay et al, JCO 2006
What’s the optimal regimen
BuMel (European) vs CEM (COG)

SIOPEN HR-NBL1
BuMel vs. CEM. Prospective Randomized, phase III study

<table>
<thead>
<tr>
<th></th>
<th>Pts</th>
<th>Events</th>
<th>3 yr EFS</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BuMel</td>
<td>281</td>
<td>136</td>
<td>49% +/- 0.03</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CEM</td>
<td>282</td>
<td>169</td>
<td>33% +/- 0.03</td>
<td></td>
</tr>
</tbody>
</table>
MIBG + BuMel

- European studies of MIBG + BuMel
- Regimen is feasible and tolerable
- Risk of SOS at higher doses (18mCi/kg)
- Encouraging responses ... small numbers
  - Overall response 5/8
  - CR in 3/8
MIBG COMBINATION
MIBG Combination Strategies

- Chemotherapy
- Radiation Sensitizer
- Increasing MIBG uptake
MIBG Combined with Chemotherapy

- **MIBG** (escalating doses) + **Irinotecan** + **Vincristine**
- Irinotecan is a radiosensitizer
- Tolerable
- MIBG up to 18mCi/kg
- Toxicities: diarrhea, liver function, hallucination
- Objective response rate of 28% all doses
MIBG Combined with Novel Agents

- MIBG alone has response rate of 30-40%
- Vorinostat is an oral HDAC inhibitor
- Vorinostat has *in vitro* and *in vivo* activity in neuroblastoma
- Vorinostat sensitizes neuroblastoma cells to radiation
- Vorinostat increases expression of the norepinephrine transporter (NET), increasing the entry of MIBG into the neuroblastoma cells.
Where is this all going?

Study Entry
Relapsed/Ref NBL
MIBG Disease

Randomize

MIBG Single Agent
MIBG + Irinotecan/V CR
MIBG + Vorinostat

Expected End 2013
MIBG UPFRONT THERAPY
Where is all this headed:
Upcoming COG High Risk NBL. Randomized phase III trial.
1st COG “MIBG-induction” study
Next Step…

- Move MIBG to upfront clinical trials
- What combination?
- Feasible to move patients around US?
- Enough centers?
- Enough production?