Use of Systemic I-131 MIBG Therapy in Advanced Malignant Pheochromocytoma/Paraganglioma Tumors

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Presenter Disclosure Information
Richard J Campeau MD

- GE Healthcare: Speaker’s Bureau & Advisory Board, Adreview™ (I-123 MIBG)

- Astellas Pharma: Speaker’s Bureau & Advisory Board, Lexiscan™

- Funded Clinical Trial Participant: Lu-177 DOTATATE in Progressive Inoperable Midgut Carcinoid Tumors
  Sponsor: Advanced Accelerator Applications
Background

- Malignant pheochromocytoma (Pheo) and paraganglioma (PGL) are rare neuroendocrine tumors that are difficult to detect; patients commonly present with metastatic disease.

- These patients with widely metastatic disease have limited treatment options.

- Surgical debulking & α-receptor blocking agents are the mainstays of palliative therapy.
Background

Additional palliative therapies for well differentiated metastatic neuroendocrine tumors:

• Systemic therapies – chemotherapy, interferon alpha, etc. have met with limited success

• Targeted tumor therapies: Chemo, bland, and radioembolization with Yttrium-90 microspheres, IV and IA I-131 MIBG therapy
What is MIBG?

- Meta-iodobenzylguanidine (MIBG) is a novel norepinephrine analog synthesized by Short & Darby in 1967. It is radiolabeled with I-123 or I-131, and taken up by ~ 90% of Pheo/PGL tumors

- I-131 radiolabeled MIBG is used as a tumor targeted therapy; it is thought to cause sterilization of tumor cells via β particle emission of internalized radiation
Sympathetic Neuron Synapse

PRESYNAPSE

Axon →

NE → NE → NE → NE → NE → NE

Vesicles

NE release into synaptic space

POSTSYNAPSE

Myocyte →

Post synaptic receptors

α₁ β₁ β₂

NE

G → G

AC → cAMP

Sympathetic Neuron Synapse

Tyrosine → Dopa → Dopamine → Norepinephrine
Development of mIBG for Neuronal Imaging

- mIBG was originally developed by DM Wieland, Ph.D. in 1978 to image the adrenal medulla in dogs (JNM 1979)
  Early studies showed uptake also in salivary glands, liver, and heart

- Mid-1980s: used as a diagnostic agent for neural crest tumors
  Became established in US and Europe
*I

meta-iodobenzylguanidine (MIBG)

[^11C]meta-hydroxyephedrine (HED)

[^11C]epinephrine (EPI)
First Cardiac I-123 MIBG Study in a Dog

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Mechanism of Interference</th>
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<tbody>
<tr>
<td>Tricyclic antidepressants, cocaine, labetalol</td>
<td>Inhibition of uptake-1</td>
</tr>
<tr>
<td>Reserpine, tetrabenazine</td>
<td>Inhibition of vesicular uptake</td>
</tr>
<tr>
<td>Norepinephrine, serotonin, guanethidine</td>
<td>Competition for vesicular uptake</td>
</tr>
<tr>
<td>Reserpine, guanethidine, labetalol, sympathetic amines (e.g., phenylpropanolamines, anorectics)</td>
<td>Depletion of content from storage vesicles</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>Calcium mediated</td>
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Complete Radiographic Response
Malignant PGL with Liver Metastases


Whole Body I-131 MIBG Scan

Anterior

Posterior
I-131 MIBG Therapy at OMCK

Two pathways at OMCK:

1.) IND for Azedra® Trial (Sponsor: Molecular Insight Pharmaceuticals, Cambridge, MA) Specific phase 3 drug study for malignant pheochromocytomas – D/C’ed by Sponsor, MIP

2.) Non IND: Done as “practice of medicine” (POM)

A prescription is written by an Authorized User (AU) to a radiopharmacist to compound x mCi of I-131 MIBG
I-131 MIBG Therapy at OMCK

Pheos/ PCL tumor patients qualify if:

- They show progressive disease (PD) after conventional therapies, including surgery, chemo with CVD, bland and chemoembolization, RFA, etc.
- They demonstrate avid I-123 MIBG uptake, 2-3x background in all or most all lesions
- They have a reasonable heme profile PL > 80K
- They have good LFTs (bili < 2 x ULN)
I-123 MIBG
I-131 MIBG Therapy at OMCK

Neuroendocrine tumor patients with PD who qualify get:
- Admission to the hospital (isolation room)
- Thyroid blockade, hydration 150cc/hr NS
- Receive 7.4 GBq (200 mCi) I-131 MIBG over 0.5-1 hr via lead shielded IV pump at bedside. Repeated at 10-12 weeks for total of at least 3 cycles (~ 22.2 GBq)
- VS, SEs monitored; Rad safety precautions
I-131 MIBG Therapy

- I-131 compounded with MIBG by (Nuclear Diagnostic Products – NJ)
- Received frozen – in dry ice
- Thawed; Q/C done (Sepak)
- ~ 1:00 PM dose is infused over 1 hour with VS q 15 minutes x 2 hrs then routine
Plastic Covering

- Prevent objects from becoming contaminated
- Allows faster clean-up after patient leaves
I-131 MIBG Cart

- Lead shielding
- Infusion pump
- Absorbent pads
- Cart is kept in the “MIBG hot lab”
Bed Shields

- 2” of lead
- Use 2-3 shields
- Protects staff
- Reduce radiation levels in adjacent areas
Protective Clothing

- Booties – when entering room
- Gloves and gowns – when caring for patients or handling urine, etc
- Remove at door when exiting
Personnel Dosimeter Use

- Measures cumulative exposure
- Must wear when entering room
- Record readings in log book at patient’s door
Waste Boxes

- Put all linens in one waste box for decay if contaminated.
- Perishables (food, etc) in another – which is decayed in a freezer in the MIBG “hot lab”
I-131 MIBG Therapy at OMCK

Pts can be released when rad survey monitor shows <7mR/hr @ 1m - usually 36-48 hrs

Retreated @ 10-12 weeks for at least 3 cycles (to a cumulative dose of at least 22.4 GBq (600mCi))

Follow Up: CBC, CMP q 2-3 wks x 4; tumor markers: CgA, plasma catecholamines, plasma/urine fractionated metanephrines q 3 months. CT/ MRI and I-123 MIBG scans q 6mo for first year, then yearly
I-131 MIBG Side Effects

- N/V uncommon – we use Zofran or other antiemetics
- Temporary myelosupression – generally mild; however, we have seen 2 grade 4 heme toxicities – one in a pt heavily pre-Rx’ed with chemotherapy
- HTN episodes – uncommon, but have parenteral nifedipine (Procardia), 10 mg available
- Hypothyroidism – can occur even w/ SSKI blockage
I-131 MIBG Rx: Future

- I-131 MIBG now widely recognized as an effective Rx for patients with malignant pheo/PGL.

- While lower dose MIBG (<300mCi) has been used extensively for Rx of malignant pheo/PGL, complete remission (CR), and sustained partial remissions (PR) have been rare at these doses, especially among patients with bone metastases.
Experience to date, at centers both in Europe and the US suggests that to achieve a remission, sufficient doses of I-131 MIBG must enter tumor cells.

In the past, high dose MIBG therapy was not possible due to dangers of myelosuppression. Now peripheral blood stem cell leukaphoresis & cryopreservation has made it possible to treat these malignancies more aggressively.
MIBG Study - Methods

- A retrospective chart review was performed in 8 patients who underwent sixteen I-131 MIBG treatments from March, 2012 through February, 2014.

- Eligibility: Patients had to show intense uptake of I-123-MIBG on scans, and had to demonstrate progressive metastatic disease after surgical/medical therapies.
Methods (cont.)

• Patients were analyzed pre and post MIBG therapy via tumor marker response utilizing conventional biomarkers CGA, plasma and 24 hr urine fractionated metanephrines, and plasma catecholamines

• Radiographic response was evaluated with RECIST 1.1 (2009) criteria

• Symptomatic response was evaluated with quality of life questionnaires (Karnofsky score and modified EORTC QLQ C-30) as well as telephone contact as appropriate
Results

• A favorable biochemical response after MIBG therapy was seen in 75% (6 of 8 evaluable patients). No deaths have yet occurred in this group.

• Seven of 8 (88%) patients with elevated tumor markers showed reductions of > 50% in either CGA and/or plasma/urine metanephrines.

• Only 1 of these 8 patients (13%) has shown progression of metastatic disease (bone) during this 2yr study period.
Results (cont)

• Radiographic tumor response before and after MIBG treatment could be evaluated in all 8 patients.

• Seven of 8 patients (88%) showed sustained responses (CR, PR, and SD) over the study period.

• None of the patients showed radiographic progression of disease (via RECIST criteria). One of these 8 patients demonstrated progression in non-measurable disease, i.e. new bone metastasis.
Conclusions

• In this small group of malignant pheo/PGL patients, significant decreases in tumor markers occurred after I-131MIBG treatment.

• Seven of 8 patients also showed stable radiographic disease, both of which has correlated with a favorable short term outcome.

• This small study will be extended with high dose I-131 MIBG therapy in these rare malignancies.