New and Approved:
Review of Radiopharmaceutical Therapies

EB Santos MD PhD and Krisztian Sandidge
131I-Iobenguane for the Treatment of Pheochromocytoma and Paraganglioma

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CPE Information

• Target Audience: Pharmacists
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• Activity Type: Knowledge-based
EB Santos MD PhD, has no financial or other conflicts of interest to disclose
CPE Information

• Target Audience:
• ACPE#:
• Activity Type:

(APhA will complete this information.)
Learning Objectives

- To know the clinical indication and use of $^{131}$I-lobenguane (Azedra).
- To understand the basic biology of $^{131}$I-lobenguane and its possible side effects.
- To review clinical trial findings.
- To know pertinent guidelines in dispensing and administering $^{131}$I-lobenguane.
1. A 13 year-old male with an incidental finding of a left adrenal solid mass on routine renal ultrasound (to rule out pyelonephritis). Contrast-enhanced CT of the chest, abdomen, and pelvis showed a 4.5 x 3.0 cm well-circumscribed left adrenal mass without evidence of regional nodal or distant metastasis. Left adrenalectomy was performed without complications and without sequela. Pathology revealed pheochromocytoma. On routine imaging follow up six months post surgery, a vague enhancing soft tissue density was seen on CT that thought to be related to post surgical changes. There was no other abnormalities seen in the chest, abdomen, and pelvis. MRI was done but it showed indeterminate findings partly due to movement artifacts. $^{123}$I-MIBG whole body planar and SPECT-CT scans showed MIBG-avid soft tissue within the left adrenalectomy site. In addition, multiple foci of uptake were seen within the liver and an MIBG-avid 1.1 cm portal node. FNAB of one of the liver foci showed metastatic pheochromocytoma. Systemic chemotherapy was contemplated but $^{131}$I-lobenguane (Azedra) therapy was being considered. Which of the following clinical component will be considered in Azedra therapy for this patient:

A. Patient’s age (13 years old).
B. MIBG-positive lesions.
C. Lack of metastases proof on CT.
D. Requirement of systemic chemotherapy.
2. Which of the following is NOT a trait of MIBG/Iobenguane:

A. MIBG is similar to norepinephrine and is a substrate for the norepinephrine transporter on the surface of neuroendocrine tumor cells.

B. MIBG can readily be labeled with radioiodine suitable for both diagnostic and therapeutic applications of neuroendocrine tumors.

C. $^{131}\text{I}$-MIBG is approved to be used in imaging of neuroendocrine tumors, and has been used on a compassionate basis for therapy.

D. Azedra (Iobenguane I 131) has similar high specific activity with conventional $^{131}\text{I}$-MIBG.
3. Pheochromocytoma and paraganglioma (PPGL) are neuroendocrine tumors that have:

A. No FDA-approved therapies for the treatment of metastatic, recurrent, or unresectable PPGL.
B. Older patients more commonly affected.
C. Less than 20 signs and symptoms specific for PPGL.
D. A 5-year survival rate (malignant pheochromocytoma) of more than 50%.
4. These are some of the factors to be considered before dispensing and administering $^{131}$I-lobenguane EXCEPT:

A. Pregnancy status of a patient in reproductive age group.  
B. Patient’s hydration status.  
C. Antiemetics and antidiarrheal pre-treatment medications.  
D. Thyroid blockade.
“\(^{131}\)I-lobenguane is a radioactive therapeutic agent indicated for the treatment of adult and pediatric patients 12 years and older with iobenguane scan positive, unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma who require systemic anticancer therapy.”
Neuroendocrine tumors: Incidence
Very rare tumors in an already rare category\textsuperscript{1,2}

**Annual incidence in the US (per million)**

<table>
<thead>
<tr>
<th>All cancers\textsuperscript{1}</th>
<th>Rare cancer\textsuperscript{1}</th>
<th>Neuroendocrine tumors\textsuperscript{3}</th>
<th>GEP-NETs\textsuperscript{4}</th>
<th>Neuroblastoma\textsuperscript{5}</th>
<th>PPGL\textsuperscript{6-8}</th>
</tr>
</thead>
<tbody>
<tr>
<td>5180</td>
<td>673</td>
<td>53</td>
<td>27</td>
<td>10.5</td>
<td>2-8</td>
</tr>
</tbody>
</table>


**GEP-NETs**
Gastroenteropancreatic NETs (GEP-NETs) also known as carcinoids are derived from neuroendocrine cells occurring anywhere along the gastrointestinal tract\textsuperscript{9}

**Neuroblastoma**
Neuroblastoma originates in the adrenal medulla and paraspinal or periaortic regions where sympathetic nervous system tissue is present\textsuperscript{5}

**PPGL**
Pheochromocytomas and paragangliomas (PPGL) arise from adrenal medullary chromaffin cells and extra-adrenal sympathetic neurons, respectively\textsuperscript{10}
Pheochromocytoma and paraganglioma are a rare and diverse subset of neuroendocrine tumors

- Pheochromocytoma and paraganglioma are neuroendocrine tumors originating from neural crest-derived chromaffin cells of the adrenal medulla (PHEO), and extra-adrenal sympathetic and parasympathetic paraganglia (PGL)\(^1,2\).
- PHEO/PGL tumors may be found in many locations in the body\(^3,4\).

\[\text{PHEO: 80–85\% Arise from chromaffin cells of the adrenal gland}^{2,5}\]

\[\text{PGL: 15–20\% Arise in sympathetic chromaffin tissue or non-chromaffin parasympathetic tissues}^2\]

PPGL is a rare disease

Approximately 10-35% of PPGLs are metastatic and/or locally-invasive at initial diagnosis or treatment

There are no FDA-approved therapies for the treatment of metastatic, recurrent, or unresectable PPGL

Non-approved therapeutic options include

- Chemotherapy regimen: Cyclophosphamide, vincristine, and dacarbazine (CVD)
- Conventional, low-specific-activity $^{131}$I-MIBG therapy at high doses
Metastatic or Recurrent or Unresectable Pheochromocytoma and Paraganglioma

• More than 100 symptoms and signs have been described in association with these tumors:
  • Hypertension, headaches, palpitations, and diaphoresis

• Patients often present with large tumors and/or distant metastases

• The most common locations of metastatic spread are the lymph nodes, bones, liver, and lungs

• No approved treatment

• The 5-year survival rate of patients with malignant pheochromocytoma has been reported to be as low as 11.8%¹

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Frequency %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headaches</td>
<td>60-90</td>
</tr>
<tr>
<td>Palpitations</td>
<td>50-70</td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>55-75</td>
</tr>
<tr>
<td>Pallor</td>
<td>40-45</td>
</tr>
<tr>
<td>Nausea</td>
<td>20-40</td>
</tr>
<tr>
<td>Weight loss</td>
<td>10-20</td>
</tr>
<tr>
<td>Flushing</td>
<td>20-40</td>
</tr>
<tr>
<td>Fatigue</td>
<td>20-40</td>
</tr>
<tr>
<td>Anxiety - Panic attacks</td>
<td>25-40</td>
</tr>
<tr>
<td>Sustained hypertension</td>
<td>50-60</td>
</tr>
<tr>
<td>Paroxysmal hypertension</td>
<td>30</td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>10-50</td>
</tr>
</tbody>
</table>
Survival rate varies based on the sites of metastases

Though there are no definitive markers for malignant tumors, there are various factors that tend to be associated with high risk of metastatic disease:

- Presence of an SDHB mutation
- Larger tumor size
- Younger patient age
- Increased levels of plasma methoxytyramine, a metabolite of dopamine

For patients with malignant PHEO/PGL, there is currently no cure

- Malignancy, as signaled by the presence of distant metastases, means that surgical cure is no longer an option
- Prognosis for patients with metastatic disease can be poor
- Survival rates vary greatly based on a number of factors
- The 5-year overall survival rate of patients with malignant pheochromocytoma varies between 20% and 60%, and has been reported to be as low as 12%

The 5-year overall survival rate of patients with malignant pheochromocytoma can be as low as 12%

MIBG is a well-recognized, specific targeting agent for neuroendocrine tumors

- MIBG is similar to norepinephrine and is a substrate for the norepinephrine transporter, which is highly expressed in tumor cells of neural crest origin
- MIBG binds specifically to the norepinephrine transporter on the surface of neuroendocrine tumor cells, such as metastatic/malignant pheochromocytoma and paraganglioma, and is then sequestered into vesicles
- MIBG can readily be labeled with radioactive isotopes of iodine; suitable for both diagnostic and therapeutic applications for neuroendocrine tumors

VMAT: Vesicular monoamine transporters

Excess non-therapeutic MIBG increases the risk of cardiovascular side effects and limits radiation dose

- Conventional, low-specific-activity $^{131}$I-MIBG preparations contain predominately unlabeled MIBG

- Excess unlabeled or non-therapeutic MIBG has been shown to increase the risk of cardiovascular side effects, e.g., severe acute hypertension during or immediately after infusion\(^1\) due to disruption of normal norepinephrine reuptake\(^2,3\)

- Excess non-therapeutic MIBG may also compete with the uptake of $^{131}$I-MIBG, reducing the radiation dose absorbed by the tumors\(^2\)

Patients frequently endure symptoms for years before a definitive diagnosis is reached

- Because symptoms are vague and frequent, there is an average delay of 3 years between the onset of symptoms and final diagnosis\(^1\)
- Approximately 15% of PHEO/PGL are metastatic/malignant at diagnosis
- Up to 25% of PHEO/PGL are discovered incidentally during imaging studies for unrelated disorders, with the other 75% discovered after the development of symptoms\(^1,2\)
- A portion of PHEO/PGL cases go undiscovered until death, with over 50% of all PHEO/PGL found at autopsy not clinically suspected\(^3\)

MIBG scintigraphy is particularly useful in PHEO/PGL

- MIBG can be labeled with radioactive iodine for diagnostic or therapeutic purposes\(^1,2,3\)
  - I-123 MIBG is approved to be used in imaging of neuroendocrine tumors
  - I-131 MIBG is approved to be used in imaging of neuroendocrine tumors, and has been used on a compassionate basis for therapy

- Overall sensitivity and specificity of I-123 MIBG scintigraphy in PHEO/PGL are high\(^4\):
  - For PHEO, sensitivity is 84%, and specificity is 73%
  - For PGL, sensitivity is 75%, and specificity is 100%

$^{131}$I is a commonly used radionuclide in Nuclear Medicine

- $^{131}$I is a commonly used therapeutic radionuclide
  - $^{131}$I has been used in the treatment of thyroid cancer and disorders for over 6 decades. It has well-understood radiation toxicity profiles$^{1,2}$ and well-established safety management plans

- $^{131}$I has ideal physical characteristics for a therapeutic radionuclide$^1$
  - $^{131}$I has a high linear energy, allowing very high ionization per length of travel$^1$
  - $^{131}$I has a maximum soft tissue penetration of 2.4 mm$^1$
  - Furthermore, the 8-day half-life allows flexibility for labeling purposes at a commercial radiopharmacy and shipment to a treatment facility$^3$

AZEDRA® (iobenguane I 131)

- AZEDRA is a high-specific-activity I-131 MIBG manufactured by the Ultratrace® process using a solid-phase precursor
- The drug product has high specific activity (minimal unlabeled MIBG)

<table>
<thead>
<tr>
<th>Similarities</th>
<th>AZEDRA (iobenguane I 131)</th>
<th>Conventional I-131 MIBG</th>
</tr>
</thead>
</table>

**Chemical Structure**  
MIBG is labeled at the meta position

**Mechanism of Action**  
Substrate for the norepinephrine transporter (NET)

**Differences**  
<table>
<thead>
<tr>
<th>AZEDRA (iobenguane I 131)</th>
<th>Conventional I-131 MIBG</th>
</tr>
</thead>
</table>

| Manufacturing process | From solid phase precursor  
“Ultratrace” process | By simple isotope exchange method |
|-----------------------|------------------------|----------------------------------|
| Specific activity of final drug product | ~92.5 MBq/μg (very high) | ~ 1.59 MBq/μg
1 (low) |
| Chemical mass of MIBG in a 18.5 GBq (500 mCi) dose | ~0.2 mg | ~12 mg |

AZEDRA® (iobenguane I 131) in Patients with Malignant, Recurrent and/or Unresectable Pheochromocytoma or Paraganglioma (PPGL): Updated Efficacy and Safety Results from a Multi-Center, Open-Label, Pivotal Phase 2 Study

This pivotal trial is the largest prospective study of patients with advanced PHEO/PGL to date

<table>
<thead>
<tr>
<th>Study Design</th>
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<tbody>
<tr>
<td>• Phase 2, multi-center, open-label, single-arm study</td>
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<table>
<thead>
<tr>
<th>Key Inclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• At least 12 years of age</td>
</tr>
<tr>
<td>• Diagnosis of PPGL</td>
</tr>
<tr>
<td>• Ineligible for curative surgery, failed prior therapy or not candidates for chemotherapy</td>
</tr>
<tr>
<td>• MIBG-avid</td>
</tr>
<tr>
<td>• On a stable antihypertensive medication for at least 30 days</td>
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</tbody>
</table>
Trial endpoints were selected to specifically address the dual goals of treating advanced PHEO/PGL

<table>
<thead>
<tr>
<th>Key Efficacy Endpoints</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary endpoint</strong></td>
<td>▪ Proportion of subjects with a reduction (including discontinuation) of all antihypertensive medication(s) by at least 50% for ≥6 months</td>
</tr>
</tbody>
</table>
| **Key secondary endpoints** | ▪ Objective tumor response by RECIST 1.0  
                         ▪ Tumor biomarker response  
                         ▪ Overall survival up to 5 years post-first therapeutic dose  
                         ▪ Safety |

<table>
<thead>
<tr>
<th>Study Duration</th>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>12-month efficacy phase followed by 4-years long-term follow-up</strong></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosimetric dose: 111-222 MBq (3-6 mCi)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Up to 2 therapeutic doses, each at ~18.5 GBq (500 mCi) (or 296 MBq/kg [8 mCi/kg] for patients ≤62.5 kg), approximately 3 months apart</strong></td>
<td></td>
</tr>
</tbody>
</table>
Trial endpoints were selected to specifically address the dual goals of treating PHEO/PGL

- Patients endure significant burdens resulting from hormonal dysfunction and tumor progression

### Dual Treatment Goals

**Primary Endpoint**
- Reduction or discontinuation of antihypertensive medication by at least 50% for at least six months

**Secondary Endpoint**
- Objective tumor response, assessed radiographically per RECIST 1.0

Many patients require multiple medications to manage symptoms caused by tumor-associated catecholamine hypersecretion.

Tumor burden can lead to symptoms, repeat surgery, and is the leading cause of death in PHEO/PGL.
The AZEDRA pivotal trial is the largest prospective study of patients with advanced PHEO/PGL to date

Enrolled (N=81)

- Received Dosimetric Dose (N=74)
  - MIBG scan negative (N=5)
  - Early withdrawal (N=1)
- Received 1st Therapeutic Dose (N=68)
- Received 2nd Therapeutic Dose (N=50)
- Completed the Efficacy Phase (N=45)

Did not meet eligibility criteria (N=7)

Discontinued from Efficacy Phase (N=23)

LTFU phase

Completed/Continuing in LTFU (N=16)\(^1\)

\(^1\)Analysis cutoff: Dec 11, 2017.
### Demographics and Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Dosed (N=74)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prior Treatments, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Includes Surgery</td>
<td>66 (89.2)</td>
</tr>
<tr>
<td>Includes Conventional I-131 MIBG</td>
<td>22 (29.7)</td>
</tr>
<tr>
<td>Includes Chemotherapy (CVD and/or others)</td>
<td>28 (37.8)</td>
</tr>
<tr>
<td><strong>Number of Prior Treatment Modalities, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>One</td>
<td>20 (27.0)</td>
</tr>
<tr>
<td>Two</td>
<td>26 (35.1)</td>
</tr>
<tr>
<td>Three</td>
<td>20 (27.0)</td>
</tr>
<tr>
<td>Four</td>
<td>6 (8.1)</td>
</tr>
<tr>
<td>None documented</td>
<td>2 (2.7)</td>
</tr>
<tr>
<td><strong>Location of Metastases, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>40 (62.5)</td>
</tr>
<tr>
<td>Lung</td>
<td>22 (34.4)</td>
</tr>
<tr>
<td>Liver</td>
<td>17 (26.6)</td>
</tr>
<tr>
<td>Bone</td>
<td>39 (60.9)</td>
</tr>
<tr>
<td>Others</td>
<td>24 (37.5)</td>
</tr>
</tbody>
</table>

70% (52/74) of patients were previously treated with multiple modalities

1Based on N=64 with evaluable target lesions.
Study Results: Primary Endpoint

The primary endpoint (clinical benefit) was defined as a 50% reduction, including discontinuation, of all antihypertensive medication for at least 6 months.¹

25% of patients treated with AZEDRA achieved the primary endpoint (n=17/68)¹

32% of patients treated with two doses of AZEDRA achieved the primary endpoint (n=16/50)¹

49% of patients treated with AZEDRA reduced their use of antihypertensive medications by 50% for any duration (n=33/68)¹

Study Results: Objective Tumor Response

Overall, 92.2% of patients achieved tumor response of confirmed PR or SD

Best Confirmed Overall Tumor Response by RECIST 1.0 following AZEDRA Treatment

<table>
<thead>
<tr>
<th>Best confirmed overall tumor response&lt;sup&gt;a&lt;/sup&gt; per RECIST</th>
<th>At least one therapeutic dose (N=68)</th>
<th>One therapeutic dose (N=18)</th>
<th>Two therapeutic doses (N=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluated patients*, n</td>
<td>64</td>
<td>14</td>
<td>50</td>
</tr>
<tr>
<td>Complete response</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Partial response&lt;sup&gt;a&lt;/sup&gt;</td>
<td>15 (23.4)</td>
<td>0</td>
<td>15 (30.0)</td>
</tr>
<tr>
<td>Stable disease&lt;sup&gt;b&lt;/sup&gt;</td>
<td>44 (68.8)</td>
<td>10 (71.4)</td>
<td>34 (68.0)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>3 (4.7)</td>
<td>2 (14.3)</td>
<td>1 (2.0)</td>
</tr>
<tr>
<td>No assessment</td>
<td>2 (3.1)</td>
<td>2 (14.3)</td>
<td>0</td>
</tr>
</tbody>
</table>

*Patients evaluable for response by central review; No assessment signifies patients who discontinued therapy before the first scan

<sup>a</sup>Per RECIST, partial response required confirmation at a subsequent visit

<sup>b</sup>Including moderate response (MR)
Study Results: Objective Tumor Response

Overall, 98.0% of patients who received two doses achieved tumor response of confirmed PR or SD

Maximum Confirmed Reduction in Measurable Target Lesion Size by RECIST 1.0 Criteria

Of the 68 patients treated, 56 are shown who had at least one post-baseline assessment and disease measurable by RECIST 1.0 criteria
Study Results: Overall Survival (OS)

- The 12-month OS was 91% in FA patients
- Median OS was 37 months (95% CI 31, 49), and median survival appeared similar in patients with and without lung/liver metastasis at baseline (43 and 41 months, respectively)
- Median survival time was longer in patients who received two doses of AZEDRA compared to those who received only one (44 vs 18 months)

*Survival time was to the date of death, or censored at the last date the patient was known to be alive. Analysis cutoff: December 4, 2017.*
Study Results: Adverse Event Profile

- The most common (≥50%) treatment-emergent adverse events (TEAEs) in all patients who received any dose of the drug were nausea, myelosuppression, and fatigue
- No severe acute hypertension or hypertensive crises were observed in patients during or immediately following drug administration

<table>
<thead>
<tr>
<th>Adverse Event by Preferred Term</th>
<th>Treatment-related, all grade, n (%)</th>
<th>Treatment-related, grade 3-5, n (%)</th>
<th>Any AE, all grades, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>52 (70.3)</td>
<td>1 (1.4)</td>
<td>53 (71.6)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>49 (66.2)</td>
<td>28 (37.8)</td>
<td>49 (66.2)</td>
</tr>
<tr>
<td>Anemia</td>
<td>40 (54.1)</td>
<td>14 (18.9)</td>
<td>43 (58.1)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>41 (55.4)</td>
<td>28 (37.8)</td>
<td>41 (55.4)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>32 (43.2)</td>
<td>7 (9.5)</td>
<td>41 (55.4)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>39 (52.7)</td>
<td>26 (35.1)</td>
<td>39 (52.7)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>33 (44.6)</td>
<td>1 (1.4)</td>
<td>36 (48.6)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>27 (36.5)</td>
<td>0</td>
<td>28 (37.8)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>16 (21.6)</td>
<td>1 (1.4)</td>
<td>28 (37.8)</td>
</tr>
<tr>
<td>Headache</td>
<td>16 (21.6)</td>
<td>0</td>
<td>21 (28.4)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>8 (10.8)</td>
<td>1 (1.4)</td>
<td>18 (24.3)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>14 (18.9)</td>
<td>1 (1.4)</td>
<td>17 (23.0)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>11 (14.9)</td>
<td>2 (2.7)</td>
<td>16 (21.6)</td>
</tr>
<tr>
<td>Constipation</td>
<td>4 (5.4)</td>
<td>1 (1.4)</td>
<td>16 (21.6)</td>
</tr>
</tbody>
</table>

*The safety population included all 74 patients who received any dose of the drug.
Study Results: Adverse Event Profile

Hematologic Toxicity Recovery after First Therapeutic Dose

* Change in mean laboratory values over time for patients who received at least one therapeutic dose (N=68); standard deviations were excluded for clarity.

- Infection rate was not affected
- Myelosuppression reached nadir at 4–8 weeks with subsequent recovery
- Hematological supportive care was provided for 23% of treated patients and stem cell transplantation was not required

Patients in the AZEDRA safety database were heavily pretreated and had advanced disease

“\textsuperscript{131}I-lobenguane is a radioactive therapeutic agent indicated for the treatment of adult and pediatric patients 12 years and older with iobenguane scan positive, unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma who require systemic anticancer therapy.”
Administration

- Handle with appropriate safety measures.
- Intravenously as a dosimetric dose followed by two therapeutic doses administered 90 days apart.
- Pregnancy status.
- Drugs that reduce catecholamine uptake.
- Hydration.
- Thyroid blockade.
- Antiemetic.
**Administration**

- **Myelosuppression.**
  - **First Dose:** Platelets < 80,000 and ANC < 1,200/mcL.
  - **Second Dose:** Platelets < 25,000/mcL and ANC < 500/mcL. Platelets < 50,000/mcL with active bleeding. Febrile neutropenia. Pneumonitis.
Dosimetric Dose

- **Dosimetric Dose**
  - Patients weighing greater than 50 kg: 185 to 222 MBq (5-6 mCi).
  - Patients weighing 50 kg or less: 3.7 MBq/kg (0.1 mCi/kg).

- **Dosimetry and Biodistribution Assessment**
  - Acquire anterior/posterior whole body gamma camera images within 1 hour of the AZEDRA dosimetric dose and prior to patient voiding (Day 0; Scan 1).
  - Acquire additional images on Day 1 or 2 following patient voiding (Scan 2).
  - Acquire additional images between Days 2-5 following patient voiding (Scan 3).
The recommended AZEDRA therapeutic dose is based on body weight and reduced, if necessary, based on the dosimetry data. Administer a total of 2 therapeutic doses intravenously a minimum of 90 days apart.

- **Weight Based Dose per Therapeutic Cycle.**
  - Patients weighing greater than 62.5 kg: 18,500 MBq (500 mCi).
  - Patients weighing 62.5 kg or less: 296 MBq/kg (8 mCi/kg).

- **Determine if Dose Reduction Needed Based on Critical Organ Limits.**
  - If resulting estimated critical organ absorbed-dose exceeds threshold absorbed-dose (T), calculate the reduced therapeutic total activity (i.e., the cumulative activity that would be administered in 2 therapeutic cycles) using the following equation:
    - Reduced Therapeutic Total Activity= Aw × [T ÷ {Aw × D (organ)}]
## Therapeutic Dose

### Absorbed-dose Threshold Values for Radiation Toxicity in Critical Organs

<table>
<thead>
<tr>
<th>Organ</th>
<th>~1%-rate: mortality or organ failure associated with disease</th>
<th>Time to death or organ failure</th>
<th>Threshold* absorbed-dose for ~1%-rate mortality or organ failure (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red marrow</td>
<td>H-ARS mortality</td>
<td>1-2 months</td>
<td>12</td>
</tr>
<tr>
<td>Lungs</td>
<td>Pneumonitis mortality</td>
<td>1-7 months</td>
<td>16.5</td>
</tr>
<tr>
<td>Kidneys</td>
<td>Renal failure</td>
<td>&gt;1 year</td>
<td>18</td>
</tr>
<tr>
<td>Liver</td>
<td>Hepatomegaly, ascites: possible organ failure</td>
<td>0.5-3 months</td>
<td>31</td>
</tr>
<tr>
<td>Small intestine</td>
<td>GI-ARS mortality</td>
<td>6-9 days</td>
<td>40</td>
</tr>
</tbody>
</table>

*Threshold of ~0.5 Gy for both heart and carotid artery, derived from experience with external-beam radiotherapy and associated with fractionated exposure, has also been proposed to support an ~1% mortality rate of cardiovascular and cerebrovascular deaths in >10-15 years; however, uncertainty is associated with the value ~ 0.5 Gy cited for vascular disease (ICRP publication 118, p.300, Table 4.5). Consider benefits/risks to patients.
SPECT-CT

Anterior

Posterior
Summary

- There are no approved therapies in the US for PPGL patients with metastatic and/or recurrent and/or unresectable disease.

- Study IB12B, the largest prospective clinical trial to date, has demonstrated multiple clinical benefits of AZEDRA® (iobenguane I 131) treatment
  - Control of catecholamine-associated hypertension and sustained reduction of antihypertensive medications
  - Majority of patients experienced anti-tumor benefit, both primary endpoint responders and non-responders
  - Median survival of ~37 months from time of first therapeutic dose
  - Greater clinical benefits in patients who received two therapeutic doses

- The most common treatment-emergent adverse events were consistent with expected radiation-related risks of hematologic toxicities, nausea/vomiting, fatigue, and dizziness
  - Hematological toxicities resolved within 4-8 weeks and without the need for stem cell transplantation
  - No severe hypertension, hypertensive crises or acute CV side effects were observed
1. A 13 year-old male with an incidental finding of a left adrenal solid mass on routine renal ultrasound (to rule out pyelonephritis). Contrast-enhanced CT of the chest, abdomen, and pelvis showed a 4.5 x 3.0 cm well-circumscribed left adrenal mass without evidence of regional nodal or distant metastasis. Left adrenalectomy was performed without complications and without sequela. Pathology revealed pheochromocytoma. On routine imaging follow up six months post surgery, a vague enhancing soft tissue density was seen on CT that thought to be related to post surgical changes. There was no other abnormalities seen in the chest, abdomen, and pelvis. MRI was done but it showed indeterminate findings partly due to movement artifacts. $^{123}$I-MIBG whole body planar and SPECT-CT scans showed MIBG-avid soft tissue within the left adrenalectomy site. In addition, multiple foci of uptake were seen within the liver and an MIBG-avid 1.1 cm portal node. FNAB of one of the liver foci showed metastatic pheochromocytoma. Systemic chemotherapy was contemplated but $^{131}$I-Iobenguane (Azedra) therapy was being considered. Which of the following clinical component will NOT be considered in Azedra therapy for this patient:

A. Patient’s age (13 years old).
B. MIBG-positive lesions.
C. Lack of metastases proof on CT.
D. Requirement of systemic chemotherapy.
2. Which of the following is NOT a trait of MIBG/Iobenguane:

A. MIBG is similar to norepinephrine and is a substrate for the norepinephrine transporter on the surface of neuroendocrine tumor cells.

B. MIBG can readily be labeled with radioiodine suitable for both diagnostic and therapeutic applications of neuroendocrine tumors.

C. $^{131}$I-MIBG is approved to be used in imaging of neuroendocrine tumors, and has been used on a compassionate basis for therapy.

D. Azedra (Iobenguane I 131) has similar high specific activity with conventional $^{131}$I-MIBG.
3. Pheochromocytoma and paraganglioma (PPGL) are neuroendocrine tumors that have:

A. No FDA-approved therapies for the treatment of metastatic, recurrent, or unresectable PPGL.
B. Older patients more commonly affected.
C. Less than 20 signs and symptoms specific for PPGL.
D. A 5-year survival rate (malignant pheochromocytoma) of more than 50%.
4. These are some of the factors to be considered before dispensing and administering $^{131}$I-lobenguane EXCEPT:

A. Pregnancy status of a patient in reproductive age group.
B. Patient’s hydration status.
C. Antiemetics and antidiarrheal pre-treatment medications.
D. Thyroid blockade.
LUTATHERA®
(lutetium Lu 177 dotatate)

General Overview
Krisztian Sandidge
Production Manager
Learning Objectives

- LUTATHERA® (lutetium Lu 177 dotatate) General Information
- The Theragnostic Approach
- Synthesis and Dispensing of Lutathera®
- Quality Control Methods and Considerations
- Packaging and Preparation of Lutathera®
- LUTATHERA® Regimen and Administration Procedure
- Support available for LUTATHERA®
1. What is the tissue penetration of the beta radiation emitted from \( \text{Lu}^{177} \)?
   A. 10µm
   B. 10mm
   C. 2mm
   D. 60nm
2. How many types of receptors are exceptionally common in carcinoid tumors?

A. Three  
B. Five  
C. Two  
D. Ten
3. In what type of radioactive packaging is Lutathera® shipped?
   A. Excepted Package
   B. Industrial Package
   C. Type A Package
   D. Type B Package
4. What is the recommended dosage for a single infusion of Lutathera®?
   A. 50mCi
   B. 100mCi
   C. 200mCi
   D. 400mCi
LUTATHERA® General Information

• LUTATHERA®, is indicated for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) including foregut, midgut, and hindgut neuroendocrine tumors in adults.

• LUTATHERA® for the North American market is primarily supplied from the Millburn, NJ Advanced Accelerator Applications facility.
Using NETSPOT® with Lutathera® | The Theragnostic Approach

- NETSPOT®, after radiolabeling with Ga 68, is a radioactive diagnostic agent indicated for use with positron emission tomography (PET) for localization of somatostatin receptor positive neuroendocrine tumors (NETs) in adult and pediatric patients.

- Using NETSPOT® before and after cycles of LUTATHERA® treatment can help to evaluate the patient response.

- 71% of patients scanned with NETSPOT® (PET) had
LuDOTATATE manufacturing process

The Lutathera manufacturing process consists of two main steps:

1. Drug Substance Manufacturing:
   a. Hot Cells (synthesis and dispensing) preparation;
   b. Raw materials and disposable materials preparation;
   c. Drug Substance Synthesis.
2. Drug Product Manufacturing:
   a. Drug Product Formulation;
   b. Drug Product Dispensing.

Lutathera manufacturing process takes place in the following environments:

1. Synthesis Hot Cell (Grade C): synthesis of the Drug Substance;
2. Pre Chamber (Grade A): preparation of the materials and dispensing consumables;
3. Dispensing Isolator (Grade A): for Formulation/Dispensing of the Drug Product
Synthesis of Lu177-DOTATATE Drug Substance

• The Drug Substance (DS) LuDOTATATE can be manufactured by a fully-automatic synthesis module (in grade C):
  • MiniAio - (Trasis) (for batch sizes of 74 or 148 GBq)

• Synthesis approach:
Drug Product Production

Drug Product (DP) is prepared in aseptic condition in a grade A dispensing isolator using internally designed software for the formulation of the DS and dispensing following main steps:

1. Receiving DS product from the dispensing isolator;
2. Formulation of DS with Dilution Solution;
3. Sterilizing filtration prior dispensing;
4. Dispensing of QC and customer vials.

• Primarily Consideration
  • Operator Radiation Exposure
  • Manipulation of materials
  • Visual Inspection
Primary Quality Control Considerations

- pH
- Peptide Purity
  - Metal Affinity of DOTATATE
- Radiochemical Purity
  - Radiolysis
- Endotoxins
- Sterility
  - Parametric Release
Packaging of Lutathera®

LUTATHERA® is supplied as a read-to-use, 30 mL single dose vial containing 200 mCi +/- 10%
Logistics of Lutathera Shipment

Day A  
Manufacture and Shipment from Millburn

Day B  
Hospital Receipt

Day C  
Patient Infusion

6:00 AM  
Production Begins

4:00 PM  
Quality Control

6:00 PM  
Courier or FedEx Pickup

8:00 AM  
Institution Receipt

8:00 AM  
Patient Day Begins

5:00 PM  
Patient Discharge

*All times listed are EST*

- Above is an example of a LUTATHERA® shipping timeline. LUTATHERA® is manufactured and shipped from Millburn, NJ for the North American market.

- The times listed above are estimated and subject to change based upon potential delays from logistical concerns, which may be outside of AAA’s control. Delays may affect LUTATHERA® delivery and calibration.

- Initial planning of doses are confirmed two weeks ahead of infusion to ensure adequate availability of Lu$^{177}$ sources.
Treatment Regimen

- **LUTATHERA**® (lutetium Lu 177 dotatate) 7.4 GBq (200 mCi) is administered as an intravenous infusion over 30-40 minutes every 8 weeks for a total of 4 doses (4 x 200 mCi = 800 mCi)

- **In case of toxicity:** The interval between each infusion may be extended up to 16 weeks
**Pre-Treatment Antiemetic:** To help address treatment-related nausea and vomiting, an antiemetic drug should be given 30 minutes before the amino acid solution infusion.

**Concomitant Amino Acid Infusion:** An amino acid solution containing sufficient amounts of L-lysine and L-arginine is required for renal protection. This infusion must start 30 minutes before the start of LUTATHERA® (lutetium Lu 177 dotatate) infusion and must be continued during, and for at least 3 hours after LUTATHERA® infusion.

**LUTATHERA®:** Administer as an intravenous infusion over 30-40 minutes. 50 mL/hour to 100 mL/hour for 5 to 10 mins; 200 mL/hour to 300 mL/hour for the following 25 to 30 mins

Closing remarks/conclusion

• For Further information please visit www.LUTATHERA.com or contact AAA Customer Service at 1-844-DOSE-AAA (367-3222).

More information is available through AAA Regional Market Access Managers
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Assessment Questions

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