Maximal Tolerated Dose I-131 Therapy for Advanced Thyroid Cancer and Determination of Iodine Refractory Disease*
Thyroid Master Class February, 2016

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*with help from Dan Pryma, PET NM Division Chief
Case Example

- 15 y/o female presents with multiple neck nodes and thyroid mass seen by U/S and contrast CT
  - FNA of neck nodule on outside unhelpful
- 2/05 Open biopsy of neck node = metastatic papillary thyroid cancer
- 3/05 Thyroidectomy, bilateral cervical and central neck dissections at UWMC
  - 6.8 cm papillary thyroid cancer, extra thyroidal extension into soft tissue
  - 16/18 nodes, some large, in all beds, including paratracheal node in central neck nodes
  - pT4, pN1, Mx
Thyroid Cancer Case: non-contrast CT
Post-Therapy I-131 Scan (after 120 mCi)
Bulky Nodal Disease Arose During Hormone w/d

- Persistent nodes by MRI 6 months after I-131
- Suppressed Tg ~ 20 ng/mL
- Surgical de-bulking
  - 3/3 LNs +
  - Largest 2 cm
- Tg down after surgery, but still ++
Questions to Consider

• What next?
  ◦ Likely needs more I-131
  ◦ Do we withdraw her from hormone again?
Maximal Tolerated Dose I-131 Therapy for Advanced Thyroid Cancer and Determination of Iodine Refractory Disease: Outline

- The basics (standard approach to I-131 Rx)
- Maximal-tolerated dose approaches
  - Radioiodine dosimetry for thyroid CA
  - Emerging approaches and future directions
- What constitutes iodine-refractory thyroid cancer?
Indications for I-131 Therapy for Thyroid CA

- Newly diagnosed disease post-thyroidectomy
  - Thyroid remnant ablation
  - Treat residual and/or metastatic disease
  - “Adjuvant” therapy

- Recurrent thyroid cancer
  - Iodine-avid, non-resectable or metastatic iodine-avid disease
  - Empiric therapy to determine iodine avidity and I-131 responsiveness
Integrated Approach Using $^{123}$I scan and $^{131}$I Therapy

- **Low Iodine Diet**
  - 1-2 wks
- **Hormone Withdrawal**
  - (alternative = rhTSH)
- **Day 1**
  - $0.9 \text{ mg } \text{rTSH IM}$
  - $^{123}I \text{ Dx Dose}$
  - $^{123}I \text{ Scan}$
- **Day 2**
- **Day 3**
- **5-10 days**
- **Post-therapy $^{131}$I scan**
Micronodular Lung Metastases May Not be Visualized on Diagnostic Iodine Scan
.. But May be Seen on Post-Rx Scan

Pre-Therapy (3 mCi)  Post-Therapy (150 mCi)
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Dosimetry applicable to most patients
Dosimetry applicable to patient with altered safety or clearance)
Dosimetry for I-131

- **Principles**
  - Patient-specific dose calculations based upon toxicity tolerance
  - More I-131 at once more likely to control disease

- **Indications**
  - Potentially life-threatening disease
    - Distant metastases
    - (Locally aggressive disease (+/- XRT))
  - Concern for toxicity
    - Diffuse lung metastases
    - Hematologic disorder
  - Altered clearance
    - Renal dysfunction/dialysis
I-131 Dosimetry Calculations

- Goal is to determine maximum tolerable dose of I-131
- Dose-limiting toxicity
  - Bone marrow
  - Lungs (with diffuse mets)
- Measure iodine clearance
  - Whole body - uptake probe
  - Blood - blood samples
- Goals
  - < 200 rads to blood (as proxy for marrow dose)
  - < 80 mCi in the whole body by 48 hours (lung dose)
Hypothyroid I-131 Dosimetry

- Patient confirmed to be on low iodine diet and TSH > 25 µIU/ml
  - Negative pregnancy test if childbearing potential
- 4 mCi NaI-131 orally
- Blood samples and whole body counts at 2, 24, 48, 72 hours, +/- 96 hours
- At 72 hours whole body scan and neck imaging
- Patient typically admitted for inpatient therapy the following Monday
Hormone Withdrawal $^{131}$I Therapy Using Dosimetry

- Low Iodine Diet
- Hormone Withdrawal
- Week 1
- Dosimetry
- 4 mCi $^{131}$I
- Therapeutic Dose $^{131}$I
- Post-therapy $^{131}$I scan
131I Dosimetry Calculations

Whole Body Clearance

Blood Clearance

Marrow Radiation Dose

Lung Radiation Dose

Lung Uptake

Patient Size

(Buena, 1964)
Patient Name: [Redacted]
ID: 222
Pt Wt (lb): 5
Pt Ht (ft in): 5
Imaging Radionuclide: I-131

Biological Clearance

\[ \text{Blood data} \quad \text{Blood Fit} \quad \text{WB data} \quad \text{WB Fit} \]

- Blood b. clearance: \( \frac{-t(d)}{0.505} \times 2.5 \times 2 \) %uC/L
- Body b. clearance: \( \frac{-t(d)}{0.887} \times 101.1 \times 2 + 142.7 \times 2 \) %

For diffuse lung mets, MTA = \( \frac{378}{101} \) mCi
Maximum tolerated dose administration

- Inpatient in a private, shielded, wrapped room
  - Patient must stay in room, but door can be open, visitors stay at door
  - Hospital staff can enter room to attend to patient’s needs, but will minimize time spent near the patient

- Can be discharged when cleared by radiation safety
  - 24 hours after treatment for most patients
    - Can be much longer in patients with slow clearance or very high disease burden

- Post therapy scan ~ 1 week after therapy, regardless of day of discharge
Toxicity from therapy

- Most patients experience few early and no late toxicities
- With higher doses, increasing risk of:
  - Nausea
  - Hematologic toxicity
    - Nadir at 4-6 weeks after therapy (platelets)
  - Dry eyes, watering eyes, dry mouth
  - Sialoadenitis
    - Use of sialogogues is controversial
I-131 Rx of Pulmonary Metastases
Complete Remission Using Dosimetry-Guided $^{131}$I Rx

150 mCi  
2/11/00  
Widespread Metastases

400 mCi  
10/5/00  
Small Residual Dz by $^{131}$I and CT

450 mCi  
12/10/01  
$^{131}$I-131, CT, TG negative

(NB $^{131}$I Metastatic Surveys)
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rTSH-Stimulated $^{131}$I Therapy Using Dosimetry

- **Low Iodine Diet**
- **Dosimetry**
- **0.9 mg rTSH IM**
- **1-3 mCi $^{131}$I**
- **Therapeutic Dose $^{131}$I**
$^{131}$I Therapy Using rTSH Stimulation and Dosimetry

Pre-Rx Scan

Post-Rx Scan
rhTSH versus THW: Comparative Dosimetry

Comparative Residence Times

<table>
<thead>
<tr>
<th>Organ</th>
<th>Residence time (h), ICRP 53</th>
<th>rhTSH patients (n = 11)</th>
<th>Withdrawal patients (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total body</td>
<td>11.1</td>
<td>15.2 ± 3.1</td>
<td>23.0 ± 7.7</td>
</tr>
<tr>
<td>Bladder</td>
<td>1.76</td>
<td>1.3 ± 0.2</td>
<td>1.4 ± 0.7</td>
</tr>
<tr>
<td>Kidneys</td>
<td>0.13</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Rest of body</td>
<td>—</td>
<td>12.8 ± 3.1</td>
<td>20.3 ± 13.7</td>
</tr>
<tr>
<td>Stomach</td>
<td>—</td>
<td>1.5 ± 0.8</td>
<td>2.9 ± 1.9</td>
</tr>
<tr>
<td>Colon</td>
<td>—</td>
<td>4.0 ± 1.0</td>
<td>5.3 ± 1.8</td>
</tr>
<tr>
<td>Effective half-life</td>
<td>—</td>
<td>10.6 ± 2.2</td>
<td>16.0 ± 5.4</td>
</tr>
</tbody>
</table>

Urinary Excretion

Conclusion: rhTSH-driven therapy decreases radiation exposure per mCi
rTSH I-131 Scan: 15 y/o with Metatatic Papillary Thyroid CA

- Thyrogen (rTSH protocol)
- TSH < 0.03 --> 7.5
- Thyroglobulin 5 ---> 35
- Re-ultrasound to rule out bulk disease
- rTSH-driven dosimetry and I-131 Rx
Follow-Up

- No adenopathy by exam or imaging
- Stable Tg - low on suppression
- Stable CT scan
Lesional Dosimetry

- Whole body/blood-based dosimetry does not predict tumor response
- Visual assessment of tumor uptake on planar scintigraphy very inaccurate
- Determining lesional dosimetry requires of imaging:
  - High resolution
  - Sensitivity
  - Accurate quantification
Iodine-124 dosimetry

- 4 mCi sodium iodine-124 given orally
- Multiple PET scans over 3-5 days after I-124 administration
- Individual lesion kinetics can be used to determine potential therapeutic exposure to that lesion
- Whole body and blood counts can also be done to determine maximum tolerated dose
Lesional dosimetry

229 cGy/mCi

203 cGy/mCi

125 cGy/mCi

Courtesy of John Humm, PhD
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Radioiodine only works if the disease takes up radioiodine

- Thyroid cancer can lose the ability to concentrate iodine
  - Not de-differentiation
  - Potentially reversible
    - Many historical false starts

- Patients with poor iodine concentration are unlikely to benefit from radioiodine therapy
Iodine refractory: common criteria

- Target lesion without uptake on radioiodine scan
  - Diagnostic scans technically challenged
  - Uptake on post therapy scan does not guarantee a beneficial dose

- Progression of disease within 16 months after therapy
  - Interpret in context of clinical course

- Cumulative radioiodine dose > 22.2 GBq (600 mCi)
  - (Rationale for this are unclear)
Micronodular Lung Metastases May Not be Visualized on Diagnostic Iodine Scan .. But May be Seen on Post-Rx Scan

Pre-Therapy (3 mCi)  
Post-Therapy (150 mCi)
FDG Predicts Survival in Recurrent Thyroid Cancer - Robbins, JCEM, 2006

131I-

FDG PET

High TG, Neg Scan

L Cervical LN

 FDG-

p<0.001

FDG+

Surviving Fraction

At risk 314 186 94 40

Months from PET Scan

FDG - (n=180)
FDG + (n=219)
I-131 has an excellent therapeutic index for iodine-avid and sensitive thyroid cancer

Using iodine dosimetry to calculate a maximum tolerated dose presents an attractive option for:
  ° Metastatic disease
  ° Altered I-131 Clearance
Maximal Tolerated Dose I-131 Therapy for Advanced Thyroid Cancer and Determination of Iodine Refractory Disease: Summary (2)

- rhTSH-stimulation and dosimetry offers an attractive alternative to hormone w/d; dosimetry accounts for faster I-131 clearance
- I-124 PET may offer lesional dosimetry – better prediction of response
- Determination of iodine refractory disease:
  - Low or absent I-131 uptake (post-therapy scan)
  - Early progression after therapy