PRRT in patients with neuroendocrine tumors

By

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Somatostatin receptor scintigraphy

Neuroendocrine tumours:

- Carcinoids
  - Midgut  >90%
  - Bronchial  67%
- Endocrine pancreatic tumours
  - Gastrinomas  >90%
  - Insulinomas  <50%
- Paragangliomas  >90%
- Pheocromocytomas  86%
- Neuroblastomas  90%
- Medullary thyroid carcinomas  65%
## Grading of radionuclide uptake at somatostatin receptor scintigraphy

<table>
<thead>
<tr>
<th>Grade</th>
<th>Appearance of somatostatin receptor scintigraphy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td><strong>No</strong> radionuclide accumulation in known tumor lesions</td>
</tr>
<tr>
<td>1</td>
<td><strong>Suspected but not certain</strong> uptake in known tumor lesions</td>
</tr>
<tr>
<td>2</td>
<td>Accumulation in known tumor lesions, intensity less or equal to normal liver uptake</td>
</tr>
<tr>
<td>3</td>
<td>Clear uptake in known tumor lesions, higher than liver uptake</td>
</tr>
<tr>
<td>4</td>
<td>Intense uptake in known metastases</td>
</tr>
</tbody>
</table>
Targeted irradiation therapy

- $^{111}$In-DTPA$^0$-octreotide
- $^{90}$Y-DOTA$^0$,Tyr$^3$-octreotide
- $^{177}$Lu-DOTA$^0$,Tyr$^3$-octreotate
- $^{131}$I-MIBG
- $^{90}$Y-SIR-Spheres
<table>
<thead>
<tr>
<th>Isotope</th>
<th>$T_{1/2}$ (days)</th>
<th>Emissions</th>
<th>Range (average)</th>
<th>Range (max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{111}$In</td>
<td>2.8</td>
<td>$\gamma$ rays</td>
<td>Auger electrons</td>
<td>10 $\mu$m</td>
</tr>
<tr>
<td>$^{90}$Y</td>
<td>2.7</td>
<td>$\beta$ particles</td>
<td>4 mm</td>
<td>12 mm</td>
</tr>
<tr>
<td>$^{177}$Lu</td>
<td>6.7</td>
<td>$\beta$ particles</td>
<td>0.5 mm</td>
<td>2 mm</td>
</tr>
<tr>
<td>$^{131}$I</td>
<td>8.0</td>
<td>$\beta$ particles</td>
<td>$\gamma$ rays</td>
<td>0.4 mm</td>
</tr>
</tbody>
</table>

after van Essen 2007
$^{177}$Lu-DOTA-Tyr$^3$-Octreotate

Graphics: Dr Daniel Lindholm

With courtesy from Ulrike Garske
Indications:

- Carcinoids, endocrine pancreatic tumours, pheo/paragangliomas
- Grade 3–4 uptake on octreoscan
- Bone marrow and kidneys dose-limiting organs:
  - Adequate bone marrow function
  - Adequate renal function
- Bilirubin <40 µmol/L
- AST/ALT < 5 x upper reference limit
- Life expectancy >3 months
Contraindications:
- Tumours accessible to surgery or RF ablation
- Decreased bone marrow or renal function:
  - Hb <100 g/L
  - WBC <3.0x10⁹/L
  - Neutrophils <1.5x10⁹/L
  - Platelets <100x10⁹/L
  - Creatinine >110 μmol/L
  - GFR <50 ml/min
- Moderately/severely decreased liver function
- Massive liver metastases with high uptake on OctreoScan
- Inability to be isolated for 24 h
- Inability to manage the personal care
- Proliferation (Ki67) >20–30%
177Lu-DOTA-octreotate therapy
The Uppsala experience

- Sandostatin LAR discontinued 4 weeks before treatment
- Short-acting Sandostatin discontinued evening before treatment
- IntronA discontinued 1 week before treatment
- PegIntron discontinued 2 weeks before treatment
The Uppsala experience

- 262 patients (113 midgut, 14 lung, 20 rectal, 52 non-functioning EPT, 9 gastrinoma, 8 glucagonoma, 8 paraganglioma, 3 pheochromocytoma)

- 993 treatments

- Follow-up (n=208): Mean 20 months (2–70)

Results:

<table>
<thead>
<tr>
<th></th>
<th>CR</th>
<th>1</th>
<th>(0.5%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PR</td>
<td>64</td>
<td>(31%)</td>
</tr>
<tr>
<td></td>
<td>MR</td>
<td>21</td>
<td>(10%)</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>113</td>
<td>(54%)</td>
</tr>
<tr>
<td></td>
<td>PD</td>
<td>9</td>
<td>(4%)</td>
</tr>
</tbody>
</table>

43 patients with response or SD have later progressed
Treatment effect over time:

$^{177}$Lu-DOTA-octreotate 24 hrs pi

Feb 09  Apr 09  May 09  Aug 09  Jan 10  Mar 10

Posterior view planar images

Best response RECIST: -47%  PR, ongoing remission
Right kidney at 1st and 6th cycle
### Side effect

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia grade 3–4</td>
<td>5</td>
</tr>
<tr>
<td>Leucopenia grade 3–4</td>
<td>13</td>
</tr>
<tr>
<td>Neutropenia grade 3–4</td>
<td>15</td>
</tr>
<tr>
<td>Renal grade &gt;1</td>
<td>1</td>
</tr>
</tbody>
</table>

One patient died from pancytopenia
One patient developed acute leukemia
**177Lu-DOTA-octreotate therapy**

The Rotterdam experience

310 patients: 188 carcinoid, 72 non-functioning EPT, 12 gastrinoma, 5 insulinoma, 2 VIPoma, 31 unknown

Results 3 months after last administration (n=310):

<table>
<thead>
<tr>
<th>Response</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>5</td>
<td>(2%)</td>
</tr>
<tr>
<td>PR</td>
<td>86</td>
<td>(28%)</td>
</tr>
<tr>
<td>MR</td>
<td>51</td>
<td>(16%)</td>
</tr>
<tr>
<td>SD</td>
<td>107</td>
<td>(35%)</td>
</tr>
<tr>
<td>PD</td>
<td>61</td>
<td>(20%)</td>
</tr>
</tbody>
</table>

46% (CR + PR)

4% with SD or MR had further improvement at 6 months
5% with SD or MR had further improvement at 12 months

Kwekkeboom et al, JCO, 2008
177Lu-DOTA-octreotate therapy
The Rotterdam experience

• Median time to progression: 40 months
• Median OS from start: 46 months
• Median OS from diagnosis: 128 months
• Survival benefit from diagnosis: 40–72 months
• CR, PR, MR, SD longer survival

Higher remission rates:
  – high uptake on octreoscan
  – KPS >70

Shorter time to progression:
  – bone metastases
  – extensive liver involvement
  – gastrinoma/insulinoma/VIPoma tumour type

Kwekkeboom et al, JCO, 2008
177Lu-DOTA-octreotate therapy
Side effects, n=504

Acute (≤24 h):
Nausea 25% treatments
Vomiting 10% treatments
Abdominal discomfort 10% treatments
Hormonal crisis 6 patients

Subacute (4–8 weeks):
Hematologic grade 3–4 9.5% patients; 3.6% treatments
Hair loss (grade 1) 62% patients

Serious delayed toxicities: 9 patients
• renal insufficiency (2 patients)
• liver failure (3 patients)
• MDS (4 patients)

Kwekkeboom et al, JCO, 2008
Bronchial carcinoids, n= 9: 5 PR, 1 MR, 2 SD, 1 PD
Median time to progression 31 mo

Gastric carcinoids, n=5: 1 CR, 1 MR, 2 SD, 1 PD

Thymic carcinoids, n=2: 1 SD, 1 PD

Paragangliomas (n=12): 2 PR, 6 SD, 3PD, 1 not known

Conclusion: $^{177}$Lu-octreotate can be effective in patients with paraganglioma
Patients:

- 50 patients with neuroendocrine GEP tumours
- Follow-up ≥3 months
- EORTC QLQ C-30 before start and 6 weeks after last cycle

Results:

- Global health status/QoL increased from 69.0 to 78.2 (p<0.01)
- Patients with regression most frequently had improvement in QoL
- Role, emotional and social function improved significantly
- Fatigue, insomnia and pain decreased significantly

Conclusion: $^{177}$Lu-octreotate therapy improved QoL and several functions and reduced symptoms in patients with metastatic neuroendocrine tumours, but especially in those with proven tumour regression

Teunissen et al, JCO, 2004
90Y-DOTA-TOC therapy
The Basel experience

• 1,109 patients (265 small bowel, 44 large bowel, 84 lung, 295 non-functioning EPT, 25 gastrinoma, 8 glucagonoma, 8 insulinoma, 28 paraganglioma, 11 pheochromocytoma, 29 MTC, 12 SCLC)

• 2,472 treatments: 3.8 GBq/m²

• Median follow-up: 23 months

Results:
CR+PR 378 (34.1%)
SD 58 (5.2%)
Disease control 436 (39.3%)
PD 673 (60.7%)

491 patients (44.3%) died, 609 patients (54.9%) survived
Median survival from diagnosis: 94.6 months

Imhof et al, JCO 2011
### 90Y-DOTA-TOC therapy

#### Side effects

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transient hematologic grade 3-4</td>
<td>142 patients (12.8%)</td>
</tr>
<tr>
<td>Leucopenia</td>
<td>67 patients</td>
</tr>
<tr>
<td>Anemia</td>
<td>11 patients</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>64 patients</td>
</tr>
<tr>
<td>Severe permanent renal</td>
<td>102 patients (9.2%)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>67 patients</td>
</tr>
<tr>
<td>Grade 5</td>
<td>35 patients</td>
</tr>
<tr>
<td>MDS</td>
<td>1 patient</td>
</tr>
<tr>
<td>AML</td>
<td>1 patient</td>
</tr>
</tbody>
</table>

Imhof et al. JCO 2011
90Y-DOTA-TOC therapy
Proliferation index

81 patients with GEP-NETs
4 cycles of $^{177}$Lu-Octreotate 7.9 GBq

<table>
<thead>
<tr>
<th>Grade</th>
<th>n</th>
<th>Regression</th>
<th>Stabilization</th>
<th>Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>25</td>
<td>12 (48%)</td>
<td>12 (48%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>G2</td>
<td>49</td>
<td>29 (59%)</td>
<td>13 (27%)</td>
<td>7 (14%)</td>
</tr>
<tr>
<td>G3</td>
<td>7</td>
<td>1 (14%)</td>
<td>1 (14%)</td>
<td>5 (71%)</td>
</tr>
</tbody>
</table>

G1: Ki-67 index <3%
G2: Ki-67 index 3-20%
G3: Ki-67 index >20%

Tumor responses in patients with GEP tumors, treated with different radiolabelled somatostatin analogs

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Pats.</th>
<th>CR+PR</th>
<th>SD</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>$(^{111}\text{In-DTPA}^0)\text{octr}$</td>
<td>52</td>
<td>0–8%</td>
<td>62–81%</td>
<td>12–38%</td>
</tr>
<tr>
<td>$(^{90}\text{Y-DOTA}^0,\text{Tyr}^3)\text{octr}$</td>
<td>186</td>
<td>9–33%</td>
<td>52–69%</td>
<td>9–19%</td>
</tr>
<tr>
<td>$(^{177}\text{Lu-DOTA}^0,\text{Tyr}^3)\text{octr}$</td>
<td>310</td>
<td>29%</td>
<td>51%</td>
<td>20%</td>
</tr>
</tbody>
</table>

Response duration: $(^{90}\text{Y-DOTA}^0,\text{Tyr}^3)\text{octreotide}$ 30 months

$(^{177}\text{Lu-DOTA}^0,\text{Tyr}^3)\text{octreotate}$ 40 months

Kwekkeboom et al, Endocr Relat Cancer, 2010
Conclusion

• Somatostatin receptor mediated treatment provides a feasible, widely well tolerated therapeutic option for patients with neuroendocrine tumours

• beta emitters are promising

• Treatment with combination of $^{90}$Y and $^{177}$Lu may provide even better tumour control

• Best time for radioisotopes in the treatment of these patients is still to be established

• Combination with chemotherapeutic agents such as capecitabine, aiming at potentiating the effect, is interesting
Conclusion

Which patients should be treated:

- High uptake, grade 3–4, on octreoscan (> normal liver)
- Good general condition
- Normal bone marrow function
- Normal renal function
- Disease outside the liver
- Rectal/hindgut carcinoids
- Bowel carcinoids: Progression on interferon + somatostatin
- Foregut tumours: 1st line may be considered
Conclusion

Which patients should **not** be treated:

- Inhomogenous uptake on octreoscan
- Poor general condition
- Impaired bone marrow function
- Impaired renal function
- Extensive liver involvement (unless progression elsewhere)
- Candidates for surgery/RF ablation
Radioembolisation

- Liver embolization with SIR-Spheres®
- SIR-Spheres® = $^{90}$Yttrium-labelled resin microspheres
- Size $\approx 30–35 \, \mu m$
- High dose of radioactivity delivered selectively to liver metastases
- Pre-treatment angiography to clarify the vascular anatomy
- Pre-treatment scintigraphy with $^{99}$Tc macroalbumin to assess lung shunt ($\leq 20\%$)
Radioembolisation

Indications:
• Reduction of tumour burden
• Progression on conventional treatment
• Intractable symptoms: carcinoid syndrome, hypoglycemia, WDHA
• Main tumour burden confined to the liver

Contraindications:
• Major tumour burden outside the liver
• Patient suitable for surgery and/or radiofrequency ablation
• Severely impaired liver function
• Small amount of remaining healthy liver tissue
TheraSphere®          SIR-Spheres®

Slides courtesy Drs. Geschwind, Kerlan and Salem
Radioembolisation

Patients: n=148
Treatments: n = 185

Results:

CR  5 (2.7%)  No patient had side effects > grade 3
PR 112 (60.5%)
SD  42 (22.7%)
PD  9 (4.9%)

Median survival: 70 months

Conclusion: Use of yttrium-90 SIR-spheres is safe and effective

Kennedy, Am J Clin Oncol 2008