NUCLEAR MEDICINE
IN NETS

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Unicorn Foundation Neuroendocrine
Education/Support Group Meeting
North Shore Private Hospital, St Leonards
11 August 2010
WHAT IS NUCLEAR MEDICINE?

- uses medical isotopes to map physiology and pathophysiology in human body
- also known as functional or molecular imaging
- complements Radiology which displays anatomy
- 70 year history and recent rapid growth due to convergence technologies such as PET-CT.
computed tomography  FDG positron emission tomography  PET-CT

? dead or alive  maps metabolism  but where is the finding?
RADIOPHARMACEUTICAL

radiopharmaceutical

\[ \text{radiopharmaceutical} = \text{isotope} + \text{ligand} \]

administered intravenously, orally, etc

localises in target organ, or target pathology

emits gamma rays or beta rays

detected by gamma camera or PET camera with or without CT
isotopes are unstable → emissions

electrons (beta radiation) used in nuclear medicine therapy

positrons (antimatter electrons) annihilate to produce gamma rays for PET

gamma rays: photons like X-rays but originate from nucleus, not the shell
MEDICAL ISOTOPES

Diagnostic
- Tc$^{99m}$
- I$^{123}$
- Tl$^{201}$
- Ga$^{67}$
- In$^{111}$
- I$^{131}$
- Ga$^{68}$
- F$^{18}$

Therapeutic
- I$^{131}$
- Y$^{90}$
- Lu$^{177}$
- Sm$^{153}$
- Sr$^{89}$
- Rh$^{188}$
- P$^{32}$

reactor and cyclotron produced radioactive isotopes; differing half lives and different electron, positron and gamma emissions
isotope is directed to organ or target of interest via ligand

- Tc$^{99m}$ HDP: for bone scan
- Tc$^{99m}$ MIBI: cardiac perfusion scan
- F$^{18}$ FDG: PET tumour scan (glu metabolism)
- Ga$^{68}$ Octreotate: neuro-endocrine tumour scan, assessing SS receptor uptake

scan name often derived from ligand eg MIBI scan, or from target organ eg lung scan
Single Photon Emission Computed Tomography = SPECT
I-131 MIBG therapy for metastatic carcinoid tumour
Also images gamma rays arising from positron annihilations. Short half life isotopes like C$^{11}$, N$^{13}$, F$^{18}$. Map basic metabolic pathways like glucose metabolism (F$^{18}$-FDG). Now combined with CT (PET-CT).
NUCLEAR MEDICINE THERAPY

Therapy isotopes emit beta radiation, with or without gammas
- I-131
- Y-90
- Lu-177

Same principle as diagnostic Nuc Med
- ie target the isotope chemically to specific areas eg Lu-177 Octreotate (= Lutate)
NEURO-ENDOCRINE TUMOURS

- wide range of tumour types
  - carcinoid, phaeochromocytoma, meningioma, small cell lung cancer, medullary thyroid cancer, many others
- many are well differentiated, and slow growing
- wide range of treatment options
  - surgery, somatostatin treatment, chemotherapy, radiotherapy, radionuclide therapy
- Nuc Med/PET has diagnostic and therapeutic role in NETs
NUCLEAR MED IN NET

Octreotide scans
- In-111 Octreotide scan (SPECT-CT)
- Ga-68 Octreotate scan (PET-CT)

other scans eg bone scan

Lu-177 Octreotate therapy

other therapy
- I-131 MIBG therapy
- SirSphere therapy
MAKING A RADIOPHARMACEUTICAL

- isotope + link + Octreotide
- Ga-68 + DOTA + TOC
- In-111 + DTPA + Octreotide

aim: link and isotope should not interfere with binding of octreotide compound

half-life of isotope should approximately match uptake and binding characteristics of Octreotide compound
### Peptide Receptor Radionuclide Therapy: Forrer et al. Best Practice & Research Clinical Endocrinology & Metabolism. 21; 111–129, 2007

**Table 1. Affinity profiles (IC50) for human sst1–sst5 receptors of a series of somatostatin analogues.**

<table>
<thead>
<tr>
<th>Peptide</th>
<th>ss1</th>
<th>ss2</th>
<th>ss3</th>
<th>ss4</th>
<th>ss5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatostatin-28</td>
<td>5.2 ± 0.3 (19)</td>
<td>2.7 ± 0.3 (19)</td>
<td>7.7 ± 0.9 (15)</td>
<td>5.6 ± 0.4 (19)</td>
<td>4.0 ± 0.3 (19)</td>
</tr>
<tr>
<td>Octreotide</td>
<td>&gt;10,000 (5)</td>
<td>2.0 ± 0.7 (5)</td>
<td>187 ± 55 (3)</td>
<td>&gt;1000 (4)</td>
<td>22 ± 6 (5)</td>
</tr>
<tr>
<td>DTPA-octreotide</td>
<td>&gt;10,000 (6)</td>
<td>12 ± 2 (5)</td>
<td>376 ± 84 (5)</td>
<td>&gt;1000 (5)</td>
<td>297 ± 50 (6)</td>
</tr>
<tr>
<td>In-DTPA-octreotide</td>
<td>&gt;10,000 (5)</td>
<td>22 ± 3.6 (5)</td>
<td>182 ± 13 (5)</td>
<td>&gt;1000 (5)</td>
<td>237 ± 52 (5)</td>
</tr>
<tr>
<td>DOTA-TOC</td>
<td>&gt;10,000 (7)</td>
<td>14 ± 2.6 (6)</td>
<td>880 ± 324 (4)</td>
<td>&gt;1000 (6)</td>
<td>393 ± 84 (6)</td>
</tr>
<tr>
<td>Y-DOTA-TOC</td>
<td>&gt;10,000 (4)</td>
<td>11 ± 1.7 (6)</td>
<td>309 ± 135 (5)</td>
<td>&gt;1000 (5)</td>
<td>114 ± 29 (5)</td>
</tr>
<tr>
<td>DOTA-LAN</td>
<td>&gt;10,000 (7)</td>
<td>26 ± 3.4 (6)</td>
<td>771 ± 229 (6)</td>
<td>&gt;10,000 (4)</td>
<td>73 ± 12 (6)</td>
</tr>
<tr>
<td>Y-DOTA-LAN</td>
<td>&gt;10,000 (3)</td>
<td>23 ± 5 (4)</td>
<td>290 ± 105 (4)</td>
<td>&gt;10,000 (4)</td>
<td>16 ± 3.4 (4)</td>
</tr>
<tr>
<td>DOTA-OC</td>
<td>&gt;10,000 (3)</td>
<td>14 ± 3 (4)</td>
<td>27 ± 9 (4)</td>
<td>&gt;10,000 (4)</td>
<td>103 ± 39 (3)</td>
</tr>
<tr>
<td>Y-DOTA-OC</td>
<td>&gt;10,000 (5)</td>
<td>20 ± 2 (5)</td>
<td>27 ± 3 (5)</td>
<td>&gt;10,000 (4)</td>
<td>57 ± 22 (4)</td>
</tr>
<tr>
<td>Ga-DOTA-TOC</td>
<td>&gt;10,000 (6)</td>
<td>2.5 ± 0.5 (7)</td>
<td>613 ± 140 (7)</td>
<td>&gt;10,000 (6)</td>
<td>73 ± 21 (6)</td>
</tr>
<tr>
<td>Ga-DOTA-OCT</td>
<td>&gt;10,000 (3)</td>
<td>7.3 ± 1.9 (4)</td>
<td>120 ± 45 (4)</td>
<td>&gt;10,000 (3)</td>
<td>60 ± 14 (4)</td>
</tr>
<tr>
<td>DTPA-[Tyr²]octreotide</td>
<td>&gt;10,000 (4)</td>
<td>3.9 ± 1 (4)</td>
<td>&gt;10,000 (4)</td>
<td>&gt;1000 (4)</td>
<td>&gt;1000 (4)</td>
</tr>
<tr>
<td>DOTA-[Tyr²]octreotide</td>
<td>&gt;10,000 (3)</td>
<td>1.5 ± 0.4 (3)</td>
<td>&gt;1000 (3)</td>
<td>453 ± 176 (3)</td>
<td>547 ± 166 (3)</td>
</tr>
<tr>
<td>In-DTPA-[Tyr²]octreotide</td>
<td>&gt;10,000 (3)</td>
<td>1.3 ± 0.2 (3)</td>
<td>&gt;10,000 (3)</td>
<td>433 ± 16 (3)</td>
<td>&gt;1000 (3)</td>
</tr>
<tr>
<td>Y-DOTA-[Tyr²]octreotide</td>
<td>&gt;10,000 (3)</td>
<td>1.6 ± 0.4 (3)</td>
<td>&gt;1000 (3)</td>
<td>523 ± 235 (3)</td>
<td>187 ± 50 (3)</td>
</tr>
<tr>
<td>Ga-DOTA-[Tyr²]octreotide</td>
<td>&gt;10,000 (3)</td>
<td>0.2 ± 0.04 (3)</td>
<td>&gt;1000 (3)</td>
<td>330 ± 140 (3)</td>
<td>377 ± 18 (3)</td>
</tr>
</tbody>
</table>

All values are half maximal inhibitory concentration (IC50) ± SEM in nM. The numbers of experiments are in parentheses.

**Table 4. Results of the clinical application of somatostatin receptor imaging using various ligands in patients with gastroenteropancreatic neuroendocrine tumors.**

<table>
<thead>
<tr>
<th>Radioligand</th>
<th>Reported results</th>
<th>Comments</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>(⁶⁷Ga-DOTA-[Tyr²]octreotide)</td>
<td>Better than (¹⁸⁸F-DOPA)</td>
<td>Octreotide scan protocol inadequate</td>
<td>Hubalewska-Dydekczyk et al. (2006)</td>
</tr>
<tr>
<td>(⁶⁷Ga-DOTA-[Tyr²]octreotide)</td>
<td>No comparison to (¹¹¹In-DTPA)</td>
<td>Octreotide</td>
<td>Gabriel et al. (2007)</td>
</tr>
<tr>
<td>(⁶⁷Ga-DOTA-[Tyr²]octreotide)</td>
<td>PET better than other two methods</td>
<td>(¹¹¹In-DTPA)</td>
<td>Buschmann et al. (2007)</td>
</tr>
<tr>
<td>(⁶⁷Ga-DOTA-[Tyr²]octreotide)</td>
<td>Better than (¹¹¹In-DTPA)</td>
<td>Octreotide SPECT</td>
<td>Melietschläger et al. (2006)</td>
</tr>
<tr>
<td>(⁶⁷Ga-DOTA-[Tyr²]octreotide)</td>
<td>Better than (¹¹¹In-DTPA)</td>
<td>Octreotide scan protocol inadequate</td>
<td>Hofmann et al. (2001)</td>
</tr>
<tr>
<td>(⁶⁷Ga-DOTA-[Tyr²]octreotide)</td>
<td>Useful information additional to CT</td>
<td>No comparison to (¹¹¹In-DTPA)</td>
<td>Fanti et al. (2008)</td>
</tr>
<tr>
<td>(⁶⁷Ga-DOTA-[Tyr²]octreotide)</td>
<td>Better than (¹⁸⁸F-DOPA)</td>
<td>Octreotide scan protocol inadequate</td>
<td>Ambrosini et al. (2008)</td>
</tr>
<tr>
<td>(⁶⁷Ga-DOTA[1-naphthylalamin]octreotide)</td>
<td>Inferior to (¹¹¹In-DTPA)</td>
<td>Octreotide</td>
<td>Lebrali et al. (2002)</td>
</tr>
<tr>
<td>(⁶⁷Ga-DOTA[1-naphthylalamin]octreotide)</td>
<td>Inferior to (¹¹¹In-DTPA)</td>
<td>Octreotide</td>
<td>Virgolini et al. (2002)</td>
</tr>
</tbody>
</table>

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DON’T GET BOGGED IN DETAIL
OCTREOTIDE FAMILY

- different types of Octreotide
- different receptor binding
- different labelling capabilities
- Octreotate most commonly used in PET and therapy, while Octreotide most commonly used in SPECT.
- mixed formulations may evolve in future, for different tumour sub-types
Indium 111. Mostly a diagnostic agent, but some previous therapy use. Auger electrons have short tissue path (up to 10 microns)

Y-90: high energy electrons, with tissue penetration of up to 12mm. No gammas so less radiation concerns for bystanders

Lu-177: mid energy electrons, tissue penetration of up to 2mm. Some gammas for imaging.
OCTREOTIDE DIAGNOSTIC
SCANS

In-111 Octreotide scan with SPECT-CT is current standard, with good availability in most Nuclear Med Depts

Ga-68 Octreotate PET-CT is superior: Westmead is only provider in NSW. Referrals accepted from all Oncologists. Other states have one centre each performing Ga68-Octreotate scans.

RNSH wants to offer this service too.
OTHER NUCLEAR MED TECHNIQUES

SirSphere therapy

- used to treat liver metastases
- Y-90 labelled microspheres to embolise and give local high dose radiotherapy
- used when most of the disease is within the liver
- Westmead Hospital and St Vincent’s Private
- expensive ($8K for SirSpheres plus costs of angiogram x 2, etc)
OTHER IMAGING

- CT scanning
- MRI
- ultrasound
- plain x-rays
- angiography
- interventional procedures eg line placement
- PET: F-Dopa, F-tryptophan: no therapy analogue

All provide essential anatomic information and allow procedures to be reliably performed.
Lu-177 Octreotate

- most common peptide receptor therapy isotope used in Australia and Europe
- little used in US due to local regulations
- Lu-177 reactor produced; imported from Holland
- Lucas Heights reactor just starting to produce small amounts (first test shipments)
saline flush to check for leaks
tropisetron to block nausea + vomiting
LUTATE THERAPY

Sequential post Lutate therapy whole body scans over 16 weeks

Reduction in size and activity of carcinoid metastases
Lutate Therapy Indications

- NET
- well differentiated; Ki-67 index < 10
  (proliferative rate)
- disseminated and not surgically amenable
- progressive disease (symptoms, CT, markers eg chromogranin A)
TREATMENT PHILOSOPHY

- cure not achieved with disseminated disease by mono-therapy
- combine Lutate with biotherapy / chemotherapy
  - eg capecitabine, temozolomide, everolimus
- dose: 7.8 GBq x 4 cycles @ 8 week intervals
- expect gradual response
PATIENT PREP

day Oncology ward admission
light breakfast
22G cannula
oral benzodiazepine premed because it is a long day (can’t drive home).
4 hour amino acid infusion for reno-protection
INFUSION

- Lutate infused over 10 mins, 3.5ml of injectate made up to 10ml with normal saline
- 40 ml saline flush
- infusion via pump
- vial behind shield on trolley
- via same cannula as amino acid infusion
DISCHARGE CRITERIA

- average discharge can occur at 3.46 hours (dose rate = 25 microSv / hr at 1 m)
- 100% can go home at 6 hours
- coffee and sandwiches as soon as the patient wishes
- family member can stay with patient for day
SIDE EFFECTS

**Immediate**
- nausea and vomiting (requires IV tropisetron)
- due to AA and peptide (5m tropisetron for AA infusion, then up to 7mg for Lutate infusion at 20-30 ml)
- arm swelling (AA infusion)

**Delayed**
- side effects of chemo and radionuclide therapy only
- some marrow impairment (transient marrow suppression)
- no renal impairment

**Similar results to large published studies internationally**
Original Article

Phase II study of radiopeptide Lutetium-177-octreotate and Capecitabine therapy of progressive disseminated neuroendocrine tumors.

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Fremantle Hospital, Australia.

*Correspondence to: Dr. P. G. Claringbold, Oncology Department, Fremantle Hospital, Alma Street, Fremantle WA 6160 Australia Tel: (61 8 9431 2411); Fax: (61 8 9431 2560); E-mail: phillip.claringbold@health.wa.gov.au

Background: This phase II study investigates safety and efficacy of combination capecitabine and Lutetium-177 octreotate in treating disseminated, progressive, unresectable neuroendocrine tumors (NETs).

Patients and methods: 33 patients, with biopsy-proven NETs, positive 111Indium-octreotide scintigraphy and CT/MRI-measurable progressive disease were enrolled to receive 4 cycles of 7.8 GBq 177 Lu-octreotate, 8-weekly, with 14 days of 1650 mg/m2 capcitabine per day.

Results: 25 patients completed 4 cycles. Minimal transient myelosuppression at 3-4 weeks caused grade 3 thrombocytopenia in 1 patient but no neutropenia. Nephrotoxicity was absent. Critical organ radiation dosimetry provided median estimates to kidneys of 2.4 Gy, liver 4.8 Gy per cycle and showed cumulative doses all below toxic thresholds. Objective response rates were 24% PR, 70% SD and 6% PD. Median PFS and median OS have not been reached at a median follow-up of 16 months (range 5-33). Survival at 1 and 2 years was 91% (95% CI 75-99) and 88% (95% CI 71-96) respectively.

Conclusion: Addition of capecitabine radiosensitizing chemotherapy does not increase the minimal toxicity of 177 Lu-octreotate radiopeptide therapy and achieved ORR of 24% PR and 70% MR/SD, in patients with progressive metastatic NETs.

Key words: Neuroendocrine tumors, radiopetptide, octreotide, 177 Lu-octreotate, capecitabine.
PERTH LUTATE OUTCOMES

33 patients with biopsy proven metastatic NET, progressive despite regular therapy, unresectable.

mean age 60 years (32-82 y)

4 cycles of Lutate given

objective responses

- 24% partial response
- 70% stable disease
- 6% progressive disease

1 and 2 year survival rates: 91% and 88%
most hospitals provide In-111 Octreotide SPECT-CT service
Westmead provides Ga-68 Octreotide PET-CT scans (and F18-FDG scans for NET)
no NSW site provides Lutate therapy
radionuclide therapy business case submitted to NSW Health (for Lutate funding, plus other therapies).
LUTATE THERAPY

- Funding required for Lutate service ($1-3m per annum).
- Westmead is a suitable site for such a therapy service, but other hospitals also suitable.
- ? one or two sites in NSW
- Cost = $20-30K per patient.
- Expensive but similar in cost to sandostatin and cost offsets common.