INTRODUCING A NEW PRODUCT

INTRA-ARTERIAL APPLICATIONS OF PRRT

GS LIMOURIS

NATIONAL AND KAPODISTRIAN UNIVERSITY OF ATHENS-GREECE
On the course of the transformation of a normal to a cancerous cell the *overexpression* of already existing surface *peptide receptors* consists a very important and crucial characteristic among a plethora of morpho-functional changes of these cells.
This peptide receptor over-expression provides the possibility (a) to be used as a target site of corresponding peptides, and if these peptides can be radio-labelled, (b) to exploit the radionuclide emission for imaging (γ emission) and / or for therapeutic purposes (α, β, Auger and Internal Conversion electron emission).
The therapeutic application of the radiolabeled peptides is based on: (i) their proven internalization* into the cytoplasm and consequently (ii) their tight approach to the nucleus, in striking distance from the chromosomes, with DNA* being the fatal target within the radio-molecular emission range (a necessary and obligatory assumption for the certain chromosomal destroy).
It has been proved that besides the sst1, all other somatostatin receptor subtypes, after their binding to the radiopeptide, penetrate the cell membrane, migrate inside the cell by fluid-phase endocytosis (a process termed *internalization*) install, for unknown reasons, into the lysosomic fraction *, close to the nucleus and degrade in insoluble metabolites.
Thereafter, the empty receptor drives again to the cell membrane surface (a process termed externalization) to be further bound to another radiopeptide, being in a permanent, perpetual motion.
II. HISTORICAL CORNER
Since the discovery by Guillemin (1973) * of native tetradeca-peptide somatostatin, five specific receptor subtypes have been discovered and cloned so far. Unfortunately native somatostatin peptide has an extremely short plasma half-life (<3 min).

However, this disadvantage inspired the synthesis of analogues with more favorable characteristics, that means longer half-life (90 to 120 min) and marked smaller molecule *..
About 25 years ago, E Krenning * and D Kwekkeboom * (in Amsterdam / Rotterdam) and JC Reubi * and H Maecke * (in Bern / Basel) achieved to synthesize and further to systematically provide for diagnostic as well as for therapeutic purposes somatostatin analogs that could be labelled with In-111, Y-90 or / and recently with Lu-177.
Furthermore, they modified the labelled peptide complex by replacing the DTPA chelate with DOTA molecule * to enhance the destructive activity of the radiopharmaceutical and to increase the carrier-receptor affinity, improving the stability of the molecule.
radiolabelled SA structure in PRRT

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Chelator - aa</th>
<th>SA</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{111}$In</td>
<td>DTPA - Phe$^1$</td>
<td>OCTREOTIDE</td>
</tr>
<tr>
<td>$^{90}$Y</td>
<td>DTPA - Tyr$^3$</td>
<td>OCTREOTATE</td>
</tr>
<tr>
<td>$^{177}$Lu</td>
<td>DOTA - Tyr$^3$</td>
<td>LANREOTIDE</td>
</tr>
</tbody>
</table>
IV. TREATMENT MODALITIES FOR THE NEUROENDOCRINE TUMORS
Treatment modalities against primary or metastatic neuroendocrine tumors can be categorized as: (a) invasive i.e. surgical resection, (b) minimally invasive or ablative or locoregional, i.e. selective trans- arterial (chemo) embolization [TACE], radiofrequency ablation [RFA], laser induced thermotherapy [LITT], selective internal radio-therapy [SIRT] and (c) systemic standard therapy.
Curative surgery should be the treatment of choice, whenever possible, even in the presence of metastatic disease, including localized metastatic disease to the liver, if considered potentially resectable and the patient can tolerate the surgery.
1. The use of somatostatin analogs i.e. octreotide, pasireotide and lanreotide is a standard therapy in functioning NETs to confrontate flushing and diarrhea, being the cornerstone treatment.

2. Interferon alpha for symptom control as second line therapy due to its toxic profile.

3. Everolimus, inhibits mammalian target of rapamycin (mTOR), a serine–threonine kinase that stimulates cell growth, proliferation, and angiogenesis.

4. Chemotherapy with extremely mediocre results

5. Tyrosine kinase inhibitors: sunitinib and pazopanib
PEPTIDE RECEPTOR RADIONUCLIDE THERAPY (PRRT)
Worldwide, a plethora of references report with praising words on the impact and efficacy on NETs, treated with the aforementioned radio-molecular schemes, supported the cutting-edge importance of PRRT [especially recently after Netter-1 (**) publicity] and convincing the medical skepticism that this treatment is a trough millstone for the confrontation of this histotype of tumors.
(**) NETTER-1: A III Phase Multi-Center Study comparing the Progression Free Survival (PFS) after treatment with 177Lu-DOTA0-Tyr3-Octreotide-tate) plus best supportive care (30 mg Octreotide LAR) to treatment with High Dose (60 mg) Octreotide LAR in Patients With inoperable, midgut carcinoid tumors), as determined by Response Evaluation Criteria in Solid Tumors [RECIST] Criteria.
PRRT can be applied in both functioning and non-functioning NETs with positive somatostatin receptor scintigraphy, irrespectively of the primary tumor site and performed intravenously (i.v.) or intra-arterially (i.a.).
VII. Intravenous (i.v.) vs Intra-arterial (i.a.) PRRT Application
The disadvantage of administering intravenously (i.v.) radionuclides for therapy lies in the fact that a substantial dose proportion is dissipated within the systematic circulation and hence a reduced dose impact reaches the target *. 
On the other hand, *administering the dose intra-arterially, in the case where liver metastases are present*, after selective catheterisation of the hepatic artery as close as to them, a higher concentration percentage is expected to reach the tumour, and consequently, *a higher delivered (absorbed) dose*, and tumour destroy, with the lowest possible delivered dose to the kidneys.
The distance: dorsal vein hand system - antecubital vein up to the liver tumor is more than 3-fold longer compared to the distance: femoral artery to hepatic artery.
Often due to the consecutive catheterizations, the femoral arteries get hardened; the temporary subcutaneous implantation of a port system ending at the common hepatic artery, protects the patients from the discomfort of the catheterization process as well as from the kidney burden due to the administered contrast media.
Simple i.a. infusion vs an implantable port – system installation for i.a. infusions
the implantable permanent port system offers:

◊ stable connection mechanism
◊ higher flow rate than simple arterial catheters
◊ secure administration mode
◊ easy location of the puncture site
◊ marked reduced irradiation to critical organs
◊ QUALITY OF LIFE
Patho-physio-anatomical Background
The basic physiological principle that makes hepatic artery infusion feasible in NETs and GEP-NETs with liver metastases is the dual blood supply to the liver. The portal vein provides more than 75% of the blood flow to the normal hepatic parenchyma. Conversely, most of the blood-supply to liver metastases comes from the hepatic artery *.
Liver has dual blood supply:
- 80% portal vein
- 20% hepatic artery
Besides the mentioned liver tumor blood supply, the steadily growing interest in Radio-Molecular-Therapies is due to the advantages of successfully targeting cellular receptors in vivo with high sensitivity as well as specificity, and treatment at the molecular level; the aim of Radio-Molecular-Therapies is to selectively (α) irradiate the tumor cells, expressing sst2 and the surrounding blood vessels *, thus also (β) inhibiting the angiogenetic response * during the treatment.
According to the above, *intra-hepatic artery radio-molecular infusions* in neuro-endocrine liver metastases leads to a virtue *locoregional irradiation of the tumor* while sparing the normal liver parenchyma character, enhancing the therapeutic benefit.
The disaster which is provoked by the action of beta-radiation of Y-90 or Lu-177 or by Auger and Internal Conversion electrons of Indium-111 leads to tumor melting* and strongly suppress its function and activity.
Neuroendocrine liver metastasis of the right lobe of the liver. **Image A:** Before the onset of the therapy (size 5.88 cm) **Image B:** After the 3rd therapeutic session (size 4.28 cm).
ia vs iv infusions for nca DOTATATE

$A/A_0\%$ vs time (min)

- ia DOTATATE
- iv DOTATATE
# Tumour-absorbed dose comparison between i.a. and i.v. administration of n.c.a. Lu-177 DOTA-TATE, Lu-177 DOTA-TOC and c.a. Lu-177 DOTA-TATE

<table>
<thead>
<tr>
<th></th>
<th>i.a., n.c.a. DOTA-TATE</th>
<th>i.v., n.c.a. DOTA-TATE</th>
<th>i.v., n.c.a. DOTA-TOC</th>
<th>i.v., c.a. DOTA-TATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver dose</td>
<td>0.190 (mGy/MBq)</td>
<td>0.110 (mGy/MBq)</td>
<td>0.150 (mGy/MBq)</td>
<td>0.550 (mGy/MBq)</td>
</tr>
<tr>
<td>Tumor dose</td>
<td>33.0 (mGy/MBq)</td>
<td>12.2 (mGy/MBq)</td>
<td>13.0 (mGy/MBq)</td>
<td>4.4 (mGy/MBq)</td>
</tr>
<tr>
<td>Kidney dose</td>
<td>0.46</td>
<td>0.60</td>
<td>0.66</td>
<td>0.90</td>
</tr>
<tr>
<td>Tumor / kidney dose ratio</td>
<td>71.74</td>
<td>20.30</td>
<td>19.70</td>
<td>4.89</td>
</tr>
<tr>
<td>Red marrow</td>
<td>0.030</td>
<td>0.023</td>
<td>0.034</td>
<td>0.10</td>
</tr>
<tr>
<td>Tumor / liver dose ratio</td>
<td>173.68 (mGy/MBq)</td>
<td>110.90 (mGy/MBq)</td>
<td>86.7 (mGy/MBq)</td>
<td>8.0 (mGy/MBq)</td>
</tr>
</tbody>
</table>

*Absorbed dose estimated for a 10 g sphere mass*
### Tumour-absorbed dose comparison between i.v. and i.a. administration of [177Lu]DOTA-TATE

*Absorbed dose estimated for a 2gr sphere mass*

<table>
<thead>
<tr>
<th>Organ</th>
<th>Intra-arterial Infusion</th>
<th>Intravenous Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver dose</td>
<td>0.140 (mGy/MBq)</td>
<td>0.310 (mGy/MBq)</td>
</tr>
<tr>
<td>Tumor dose</td>
<td>48 (mGy/MBq)</td>
<td>35 (mGy/MBq)</td>
</tr>
<tr>
<td>ratio</td>
<td>342.8 *</td>
<td>112.9 *</td>
</tr>
<tr>
<td>Tumor dose / liver dose</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Tumor up% and Effective Time Comparison

<table>
<thead>
<tr>
<th></th>
<th>i.a., n.c.a. DOTA-TATE</th>
<th>i.v., n.c.a. DOTA-TATE</th>
<th>i.v., n.c.a. DOTA-TOC</th>
<th>i.v., c.a. DOTA-TATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Max up %</td>
<td>20.16</td>
<td>12.6</td>
<td>08.63</td>
<td>6.0</td>
</tr>
<tr>
<td>teff (hrs)</td>
<td>63.24</td>
<td>40.20</td>
<td>46.5</td>
<td>76.92</td>
</tr>
<tr>
<td>$R^2$</td>
<td>0.9997</td>
<td>0.9969</td>
<td>0.9895</td>
<td>0.7533</td>
</tr>
</tbody>
</table>
# Tumour-absorbed dose comparison between i.a. and i.v. administration of n.c.a. Lu-177 DOTA-TATE

<table>
<thead>
<tr>
<th></th>
<th>Intra-arterial infusion</th>
<th>Intravenous infusion</th>
</tr>
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<tbody>
<tr>
<td>Liver dose</td>
<td>0.190 (mGy/MBq)</td>
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<tr>
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<td>173.68*</td>
<td>110.9*</td>
</tr>
<tr>
<td>Tumor / kidney dose ratio</td>
<td>71.4</td>
<td>19.7</td>
</tr>
</tbody>
</table>

*Absorbed dose estimated for a 10 g sphere mass*
Amino-acid infusions (Aminosteril N-Hepa 8%, Fresenius Kabi, Germany) were in parallel applied for nephroprotection.

75 mg DTPA in 250 mL normal saline (the “Aretaieion” Protocol)* were also in parallel infused to remove free three-valent ionic contaminants from blood pool to urine.

THE MICROKOSMOS OF THE IRRADIATION AT CELLULAR LEVEL
Typical cellular diameters vary from 6 to 20 μm with the corresponding diameters of the cell nucleus ranging from 4 to 18 μm; this obviously means that DNA lies within the destroying range * of Auger (<1 μm) and internal conversion electrons (200–550 μm) of In-111, and the range of β-emission (about 6.5 mm and 2 mm) of Y-90 and Lu-177 respectively.
# Radionuclide Characteristics

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>Half Life</th>
<th>Emission</th>
<th>Mean E</th>
<th>Max. Tissue Penetration Range</th>
<th>No of Cells Destroyed / Disintegration</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{111}$In</td>
<td>2.8 d</td>
<td>$\gamma$</td>
<td>171 &amp; 245 KeV</td>
<td>0.02 – 10 μm</td>
<td>200 – 550 μm</td>
</tr>
<tr>
<td>$^{90}$Y</td>
<td>2.7 d</td>
<td>$\beta$ particles</td>
<td>2.2 MeV</td>
<td>12 mm</td>
<td>150-200</td>
</tr>
<tr>
<td>$^{177}$Lu</td>
<td>6.7 d</td>
<td>$\beta$ particles</td>
<td>497 KeV</td>
<td>2 mm</td>
<td>20-50</td>
</tr>
</tbody>
</table>

Breeman WA et al EJNM 2004;28:1421–9
III. PATIENTS’ ELIGIBILITY CRITERIA
Patients, candidates to undergo a treatment with the previously mentioned radio-labelled peptides have to fulfil the following criteria, arising after a detailed history.
First of all they have to be excluded by any other conventional treatment, considered as inefficient, that means the decision for a radiopeptide therapy has to be the most appropriate one, after meticulous laboratory examinations.
Furthermore they have to be:

(a) *positive in somatostatin receptors by biopsy and immuno-histology confirmed*,

(b) to have a *scintigraphically positive* [In-111 Pentetreotide (Octreoscan), Tc-99m Tektrotyd *in a visual scale* 4 or Ga-68 DOTATOC (if available) scans],
(c) to have a life - expectancy of more than six (6) months, a Karnofsky Index > 60,

(d) an increased serum Chromogranin-A (Cr-A) and / or a 24hr urine 5-hydroxy -indolo-acetic acid [the first is found almost always increased due to its extremely high sensitivity].
MRI pre therapy  MRI post therapy
Stage 1 (1\textsuperscript{st} to 3\textsuperscript{rd} session)
Tumor Dose $\approx 8000$ cGy

Stage 2 (4\textsuperscript{th} to 7\textsuperscript{th} session)
Tumor Dose $\approx 14000$ cGy
PRE-TREATMENT

POST 5th SESSION

UNTREATED FOR 1.5 YEAR – RECURRENCE (RELAPSE)
IV. NURSING PROCEDURE / PATIENTS' MANAGEMENT
Following the *intra-arterial* (i.a.) or *intravenous* (i.v.) application of the aforementioned 3 radio-labelled peptides, *patients have to mandatory remain for a short time* (24-48 hrs.) *in an isolated and specially designed room with toilet, entitled ‘Nursing Room for Nuclear Medicine Applications ‘*(category: A2 plus)*, according to the International Radiation Protection Rules for follow up and dosimetric reasons.
Furthermore, they should be scanned the 4 consecutive posttherapy days for dosimetric reasons. For one month, thereafter they have to complete a special follow-up questionnaire; they receive also a dosimetry certificate-report from the therapist, regarding the total dose administered in GBq and absorbed dosimetric data, in Gy, for the tumor and the main organs.
Finally, the response progress to the therapy effectiveness has to be monitored by bimonthly US-measurements and assessed exclusively by comparing CT and/or MRI images, according to the RECIST criteria, before and at least three (3) months after the end of the treatment.
VI. EFFICACY
It is known that an absorbed dose of at least 70-80 Gy must be delivered to obtain a reduction of the tumor mass (Bodei at al 2010).

De Jong at al (2002) reported that the above doses can be reached with cumulative activities of at least 7.4 GBq of 90Y-DOTA-TOC or at least 20 GBq of 177Lu-DOTAT-ATE and 40-50 GBq of 111In-DTPA-OC (Limouris at al 2008).
VII. TOXICITY
n.c.a. vs c.a. Lu-177

n.c.a. Lu-177

* higher specific activity
* higher radionuclide purity
(no 177m Lu contaminant)
* every single atom is radioactive! [75% of the c.a. Lu-177 contains the non-radioactive Lu-175 and Lu176]
Carrier-free $^{177}\text{Lu-}[\text{DOTA}^0,\text{Tyr}^3]$ octreotate blood and urinary radioactivity, expressed as a percentage of the injected dose, was significantly lower compared as to carrier-added one ($p < 0.05$); n.c.a. $^{177}\text{Lu}$-octreotate absorbed doses were (a) 8.6 fold higher for liver tumour [20 gr spherical mass], (b) 3.6 fold lower for kidneys and (c) 24.0 fold lower lower for bone marrow.
Comparison $^{177}$ Lu-DOTATATE infusions

no carrier added

carrier added

A) No carrier added showed statistically significant improved tumor to liver ratio, confirmed dosimetrically.

B) Carrier added showed marked higher kidney uptake (arrowed) and background activity.
Finally, it is important to not forget that neuro-endocrine tumors may cause endocrine syndromes related to hormonal hyper-secretion that can be dramatically exacerbated shortly after the treatment, mainly due to acute cell rupture!!!.

Furthermore and therefore, syndromes such as hypoglycemia, carcinoid and Zollinger-Ellison syndrome, must be recognized and suitably treated.
In unresectable metastatic liver lesions, positive for somatostatin receptors repeated, transhepatic, infusions of $^{90}\text{Y}$, $^{177}\text{Lu}$ and $^{111}\text{In}$ cocktails could be applied for the optimization of individualized PRRT, minimizing in parallel the toxicity in non-target tissues.

>> every isotope has its own place in treatment of NETs
The implantable permanent port system offers:

◊ stable connection mechanism
◊ higher flow rate than simple arterial catheters
◊ secure administration mode
◊ easy location of the puncture site
◊ marked reduced irradiation to critical organs
◊ QUALITY OF LIFE
Surgical resection consists the ‘gold standard’ for the treatment planning in NETs.

In cases with liver metastases, intra-arterial PRRT, after super-selective catheterization of the hepatic artery, might precede surgery in order to avoid any probable dissemination upon a scheduled excision.
up to recently about 1200 sessions were performed
Connecting with physiological saline.
Radiopharmaceutical administration procedure.
PRRT History in a Single Institute
The ‘Aretaeion’ University Hospital Protocol

The ‘Aretaeion’ Protocol consists of the exclusive trans-arterial radiopeptide infusions in solid tumors, after selective or super-selective catheterization of the hepatic artery for liver lesions or the external carotid artery for brain lesions.

Aiming to a highest possible radiation accumulation within the tumor, the protocol includes co-infusion of 50mL DTPA in 200mL of N/S in trip-drop, apart from the traditional aminoacid infusion for nephroprotection, to enhance the removal of the free ionic contaminants of the radiopeptide solution.

The protocol was the idea of our Dept since 1997 routinely performed in the Aretaeion Univ Hosp to which the name is dedicated in order to honorate the confidence and trust for this novel PRRT modality by the Surgical and Radiology Departments.

We proceeded so far to an over 700 therapeutic infusions with high doses of $^{111}$In-pentreotide transforming its diagnostic use to a therapeutic one, a small cohort of only 4 cases with $^{90}$Y-DOTATOC and 14 cases with $^{177}$Lu-DOTATATE.

Limouris et al, EJNMMI2008;35(10):
thank you very much for your attention!
Infiniment merci!