Peptide Receptor Radionuclide Therapy (PRRNT) of Neuroendocrine Tumors: The Bad Berka Approach

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prrtinfo.org
ENETS Center of Excellence Awarded March 2011
Zentralklinik Bad Berka

- Internal Medicine, Endocrinology, Gastroenterology, Oncology
  Thoracic, Abdomino/Visceral and General Surgery
  Interventional Radiology
  Nuclear Medicine & Molecular Imaging (PET/CT Center including a specialized nuclear medicine ward, medical physics and GMP radiopharmaceutical facilities/radiopharmacy center „THERANOSTIK“

- >1200 NET patient visits/year
Multidisciplinary Team at Zentralklinik Bad Berka

1 - DR. MERTEN HOMMAN, HEAD, ABDOMINAL/VISCERAL AND GENERAL SURGERY
2 - DR. ALEXANDER PETROVICH, CHIEF, INTERVENTIONAL RADIOLOGY
3 - DR. RICHARD P. BAUM, CHAIRMAN & CLINICAL DIRECTOR, CENTER FOR MOLECULAR IMAGING & THERAPY
4 - DR. DIETER HOERSCH, HEAD, INT. MEDICINE, ENDOCRINOLOGY, GASTROENTEROLOGY, ONCOLOGY
Targeted Molecular Imaging and Therapy

**THERANOSTICS**

The Key-Lock Principle

Schematic Representation of a Drug for Imaging and Targeted Therapy

**Target**
- Antigens (e.g. CD20, HER2)
- GPCRs
- Transporters

**Ligand**
- Antibodies, minibodies, Affibodies, SHALs, Aptamers
- Regulatory peptides and analogs thereof
- Amino Acids

**Linker**

**Chelator**
- $^{68}$Ga, $^{90}$Y, $^{177}$Lu

**Reporting Unit**
- $^{99m}$Tc, $^{111}$In, $^{67}$Ga
- $^{64}$Cu, $^{68}$Ga
- Gd$^{3+}$

**Cytotoxic Unit**
- $^{90}$Y, $^{177}$Lu, $^{213}$Bi
- $^{105}$Rh, $^{67}$Cu, $^{186,188}$Re

Pharmacokinetic/biodistribution modifier

Courtesy Helmut Mäcke (modified)
PRRT – The Bad Berka Concept

- **Dedicated multidisciplinary team** of experienced NET specialists
- **Selection of patients** for PRRT based on Bad Berka Score (BBS) i.e. clinical aspects / molecular features: progressive tumors, uncontrolled symptoms despite maximum conventional therapy / high SMS-receptor expression (determined by receptor PET/CT)
- **Individualized therapy plan** for each patient – no formal clinical trial
- **Frequent cycles** (4-6, up to 9) applying low or intermediate doses of radioactivity: long term low dose, not short term high dose concept
- **Combined use** of Y-90 and Lu-177 (in sequence, in few concurrent)
- **Intra-arterial PRRT** (e.g. for inoperable large primary tumors)
- **Standardized evaluation** before therapy and systematic restaging
- All clinical data are entered into a **prospective clinical database**
The Bad Berka Score (BBS): Patient Selection for Individualized PRRT

- SUV on receptor PET/CT (referrals: OctreoScan K.S.)
- Renal function (GFR and TER / creatinine & BUN)
- Hematological status (blood counts)
- Liver involvement
- Extrahepatic tumor burden
- Ki-67 index / tumor grade
- FDG status (glucose hypermetabolism of tumors/mets)
- Tumor dynamics (doubling time, new lesions)
- Karnofsky performance index
- Weight loss
- Time since first diagnosis
- Functional activity of tumor
- Previous therapies
Treatment decisions based on Ga-68 SMS receptor PET/CT
Molecular and Metabolic Imaging For Patient Selection

**Flip-Flop phenomenon:**
FDG positive, receptor negative neuroendocrine tumor

F-18 FDG
$SUV_{\text{max}}$ 15.9

Ki-67 > 30%

Poorly differentiated neuroendocrine carcinoma

Patient not suitable for PRRT

Ga-68 DOTA-NOC
Selection of Patients
What must be known before PRRT to be effective?

- Histology / immunohistochemistry
  - grading, proliferation rate (Ki-67), CgA, Synaptophysin, hormone production (e.g. glucagon, gastrin, insulin)

- Receptor density – ideally determined by receptor PET/CT (or otherwise by OctreoScan)

- Kidney function – MAG3 (TER), Tc-99m DTPA

- Blood profile/chemistry – RBC, WBC, PLT, Crea, BUN
Ga-68 DOTA-NOC receptor PET/CT: SUV of primary tumors and metastases

<table>
<thead>
<tr>
<th>SUV in primary tumors and metastases (n = 1,400 studies)</th>
<th>Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary tumors</td>
<td>19.2</td>
<td>8.2 – 109</td>
</tr>
<tr>
<td>Liver mets</td>
<td>20.9</td>
<td>3.3 - 105</td>
</tr>
<tr>
<td>Lymph node mets</td>
<td>9.5</td>
<td>4.2 – 152</td>
</tr>
<tr>
<td>Bone mets</td>
<td>13.6</td>
<td>3.0 – 20.4</td>
</tr>
<tr>
<td>Brain mets</td>
<td>12.3</td>
<td>4.6 – 17.2</td>
</tr>
<tr>
<td>Lung mets</td>
<td>2.3</td>
<td>1.6 – 5.6</td>
</tr>
<tr>
<td>Abdominal mets</td>
<td>14.8</td>
<td>5.8 – 34.1</td>
</tr>
</tbody>
</table>
Pancreas NET, status post left resection of pancreas, extirpation of liver metastasis (S2), splenectomy. MRI revealed retrocrural lesion of 2.2 cm in Ø. LAR 20 mg 4 wks before.
Complete Remission 4 years after PRRT

June 4, 2010
Patient Evaluation Before PRRT

- Receptor density determined by receptor PET/CT:
- Semiquantitative measurement by SUV (Standardized Uptake Values)
- How accurate are SUV?
Immunohistochemical Validation of Somatostatin-Receptor PET/CT As In-Vivo Method For Quantification Of Receptor Density On Neuroendocrine Tumors

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² Dept. of Nuclear Medicine/PET Centre, Zentralklinik Bad Berka, Germany
³ Department of General and Visceral Surgery, Zentralklinik Bad Berka, Germany
⁴ Department of Pathology, Zentralklinik Bad Berka, Germany

EANM 2010
Method

Ga-68 DOTA-SMS PET/CT in 34 histologically documented GEP NET patients

44 surgical specimens generated

Lesions (n=14) > 1.5 cm on PET/CT were selected to avoid partial volume effect on the semi-quantitative parameters

Ileum NET

IHC Scoring for SSTR1-5
Receptor PET/CT imaging using Ga-68 DOTANOC results in accurate estimation of somatostatin receptor density in vivo.

No significant correlation between the IRS score for SSTR1, SSTR3 and SSTR4 with the semiquantitative parameters.
Selection of Patients

What must be known before PRRT to avoid possible toxicity?

- Histology / immunohistochemistry
  - grading, proliferation rate (Ki-67), CgA, Synaptophysin, hormone production (e.g. glucagon, gastrin, insulin)

- Receptor density – ideally determined by receptor PET/CT (SUV) or scintigraphy

- Kidney function – MAG3 (TER), Tc-99m DTPA

- Blood profile/chemistry – RBC, WBC, PLT, Crea, BUN
PRRT is part of the ENETS Consensus GL!

- Consensus Guidelines for the Management of Patients with Digestive Neuroendocrine Tumours
  
  **Neuroendocrinology 2006; 84: 155-215**

- A Consensus Statement on Behalf of the European Neuroendocrine Tumour Society (ENETS)
  
  **Neuroendocrinology 2008; 87 (1): 8-39**

[www.neuroendocrine.net](http://www.neuroendocrine.net)
Establishment of GMP Beta Lab

Radiopeptide Therapy Cycles
Zentralklinik Bad Berka 1999 - 2010

1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010

1 5 4 14 109 226 289 343 398 450 512 531
Radiopeptide therapy (ZKL Bad Berka)

Patients treated \( n = 883 \)

Therapy cycles \( n = 2829 \)

Lu-177 \( n = 1511 \)
Y-90 \( n = 1318 \)

Age: 4 – 84 years
Median: 59 years

As of 31. December 2010
Our youngest patient treated by PRRT (metastatic hepatoblastoma)
PRRNT – Worldwide Request 2008
# Physical Properties of Radionuclides Used for PRRT

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>$t_{1/2}$ (d)</th>
<th>Energy (keV)</th>
<th>Path length (mm)</th>
<th>Gamma (keV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{177}$Lutetium</td>
<td>6.7</td>
<td>133</td>
<td>2</td>
<td>113 (6.6%) 208 (11%)</td>
</tr>
<tr>
<td>$^{90}$Yttrium</td>
<td>2.7</td>
<td>935</td>
<td>12</td>
<td>-</td>
</tr>
</tbody>
</table>
Bad Berka Procedure for PRRT

**Studies before therapy**

- Renal scintigraphy
  - $^{99m}$Tc-MAG3
- GFR measurement
  - $^{99m}$Tc-DTPA
- Receptor PET/CT*
  - $^{68}$Ga-DOTA-NOC

**$^{90}$Y/177Lu-DOTA-TATE Peptide Receptor Radiotherapy**

- Infusion of aminoacid solution (- 0.5 until 4 hrs) plus Gelofusine
- Infusion (15 min.) of $^{90}$Y/177Lu-DOTA-TATE

**- 2 days**

**Studies under /after therapy, dosimetry**

- $^{177}$Lu-DOTA-TATE WB scan
  - [planar scans for dosimetry]
- $^{177}$Lu-DOTA-TATE-SPECT
  - of the tumor region
- Blood sampling
- Urine sampling

*Since July 2004. Previously, Tc-99m EDDA Hynic TOC (planar & SPECT) was performed.
In selected patients, also F-18 FDG and/or F-18 fluoride PET/CT is performed as well as MRI of the liver/bones
Commence AA infusion
Loading dose 100 ml

Commence gelofusin
Loading dose 1ml/Kg over 10 min

Continue gelofusin 0.02ml.Kg$^{-1}$.min$^{-1}$ for 3 hrs

1. Inject ondansetron and and Dexamethasone 8 mg each over 2 min
2. Commence Y-90 or Lu-177 DOTATATE or DOTATOC infusion (over 15-20 min.)
Lutetium-177 DOTATATE PHARMACOKINETICS
In patients without any predisposing risk factors, PRRT is safe.

LONG-TERM FOLLOW-UP (5 YEARS) OF RENAL FUNCTION AFTER 7 CYCLES OF Y-90 / LU-177 DOTA-TATE (30.29 GBQ)
2 days after PRTT…
Pancreatic NET, extensive liver mets

Female (PhD), 35 years old, active researcher in biology
Results – Overall Response ZKL Bad Berka

Patients with Progressive GEP NET before PRRT

Response to PRRT after 3 cycles

Professor Dr. Richard P. Baum, Zentralklinik Bad Berka
Impact on the clinical status of the patient

- **Improvement** of clinical symptoms in 85
  - diarrhea
  - flushing
  - pain

- **Octreotide** doses before/after PRRT: 75 % less or no Oct

- **Weight gain** of 5 % or more in underweight pts. in 95 %

- **Improvement in Karnofsky** performance scale

- **Improvement of health state** score
Overall **mean progression free survival (PFS)** in 124 patients after the first cycle of PRRT (median is not achieved) was 44 months.
DUO-PRRT (Y-90/Lu-177 DOTATATE) of Metastatic Mediastinal NET


before PRRT-1
4 GBq Y-90
SUV 15.8

3-mo after PRRT-1
4.5 GBq Lu-177
SUV 9.3

before PRRT-2
5.5 GBq Lu-177
SUV 6.9

before PRRT-3
6-mo after PRRT-3
SUV 3.4

Persisting Remission in August 2010!
Median overall survival from start of DUO-PRRT: 59 months (415 NET patients)

Combined Y-90 / Lu-177 DOTA-TATE PRRT

Overall Survival

Median: 59 months

Results ZKL Bad Berka
Analysis of 415 NET Patients
New Avenues to Improve PRRT in Future

- **DUO-PRRT** (already routine at our center for over 7 years)
- **TANDEM-PRRT** (concurrent Lu-177/Y-90 PRRT Kunikowska et al.)
- **Intra-arterial PRRT** (> 50 i.a. treatments up to now)
- **Combined PRRT** (in combination with other treatment modalities)
  - TACE, SIRT, RFA (Hörsch et al. ASCO 2010)
  - chemotherapy (e.g. Capecitabine, Doxorubicin)
  - kinase inhibitors (e.g. Sunitinib, Sorafenib)
  - antibodies (e.g. Bevacizumab)
- **Improved peptides** (e.g. antagonists)
- Intra-operative use of probes after PRRT with Lu-177
- Improved dosimetry and radioprotection
Future Improvement:
Intra-arterial PRRT

Regression of liver and paracolic metastases after 3 PRRT cycles

Professor Dr. Richard P. Baum, Zentralklinik Bad Berka
Restaging 5 years after 1st PRRT

42 months after 4th PRRT cycle

Patient cured!

before 1st PRRT
Summary and Conclusions

- **PRRT is effective** – even for very advanced case
  - Median overall survival (n=415 patients) from start of treatment: 59 months
  - PRRT leads to significant **improvement of clinical symptoms**
  - Cure is rarely possible - **but excellent palliation** can be achieved
  - In progressive NETs, **sequential (DUO)** or **concurrent (TANDEM)** PRRT is most effective (**highest CR / PR / SD rate**)

- Significant kidney damage can be reduced (or avoided) by extending the treatment intervals and by using lower therapy activities more frequently (**Bad Berka protocol**) as up to **10 courses given** over several years were tolerated very well by most patients (no end stage renal insufficiency).

- PRRT should only be performed at **specialized centres**, NET patients need **highly individualized interdisciplinary** treatment and long term care.
Second Announcement

1st World Congress on Ga-68 and Peptide Receptor Radionuclide Therapy (PRRNT)

THERANOSTICS – On the Way to Personalized Medicine

CONGRESS VENUE: ZENTRALKLINIK BAD BERKA, GERMANY

JUNE 23 – 26, 2011 REGISTER NOW!

www.1stWorldCongress-Ga-68.de

Early Bird Registration April 29, 2011
Late Registration June 16, 2011

Post-Congress: June 27 - 29, 2011

Training School on
PET Radionuclide Generators $^{68}\text{Ge} / ^{68}\text{Ga}$ and $^{44}\text{Ti} / ^{44}\text{Sc}$

Institute of Nuclear Chemistry
Johannes Gutenberg University Mainz

Institut für Kernchemie