THERANOSTICS – Molecular Imaging using PET/CT and Peptide Receptor Radionuclide Therapy (PRRT) of Neuroendocrine Tumors

Prof. Dr. med. Richard P. Baum
Zentralklinik Bad Berka GmbH, Klinik für Nuklearmedizin und PET-Zentrum

Objectives
1. Definition of THERANOSTICS, personalized and precision medicine
2. Indications for Ga-68 somatostatin receptor [SSTR] PET/CT in neuroendocrine tumors (NET): staging, restaging, detection of unknown primary tumors
3. Molecular imaging (quantification of receptor density by SUV measurements) for selection of NET patients for PRRT and therapy response evaluation after PRRT by Ga-68 SSTR PET/CT
4. Indications for PRRT, methodology and clinical results (survival, PFS in patients with G1/G2 NET)
5. Possible adverse effects of PRRT and how to reduce/avoid side effects
6. Future developments: new peptides (e.g. SSTR antagonists, CXCR4)

The strong expression of SSTR2 by neuroendocrine tumors (NETs) enables peptide receptor radionuclide therapy (PRRT), the molecular internal radiation therapy of NETs. The most important points to consider for PRRT are:

- Patient selection
- Appropriate choice of peptide and radionuclide
- Kidney protection
- Tumor and organ dosimetry (post-treatment scans) and
- Monitoring of toxicity (follow-up).

In our hospital, which was certified as ENETS Center of Excellence in March 2011 and re-certified in Dec. 2013, a dedicated multidisciplinary team of experienced NET specialists is responsible for the management of NET patients (over 1,100 patient visits per year).

Patient selection for PRRT is based on the Bad Berka Score (BBS) which takes into account clinical aspects and molecular features. The therapy plan for each patient is individualized.
Frequent therapy cycles (4-6 and up to 8), applying low or intermediate doses of radioactivity are suitable for these relatively slow-growing tumors (“long term low dose, not short term high dose concept”).

For kidney protection, patients are well hydrated and receive an amino acid infusion containing lysine and arginine given intravenously for 4 hours beginning 30 minutes before PRRT. Renal function is serially determined by Tc-99m MAG3 scan/TER and by Tc-99m DTPA (GFR) measurements.

Before each new treatment cycle, restaging is performed by morphologic (CT/MRI) and molecular imaging (Ga-68 SSTR PET/CT, in selected cases F-18 FDG or F-18 fluoride PET/CT studies are additionally performed), blood chemistry and tumor markers. All data are entered in a prospective structured database.

Another very important aspect is dosimetry. Estimation of tumor and normal organ doses performed after PRRT (using Lu-177 labeled somatostatin analogues DOTATATE or DOTATOC) is important to ensure that maximum dose is delivered to the tumors and therefore optimizing an individualized treatment protocol.

**NET Center Bad Berka - Overall Results**

Retrospective analysis was performed using our database in 1000 patients (age 4 - 85 years) with metastatic and / or progressive NETs, undergoing 1 - 10 cycles of PRRT at our center using Lu-177 (n=331), Y-90 (n=170) or both (n=499). Median total administered activity was 17.5 GBq. They were followed up for up to 132 months after the 1st cycle of PRRT. Well-differentiated NETs (G1-2) accounted for 54%. Most patients (95.6%) had undergone at least 1 previous therapy (surgery 86.8%, medical therapy 55%, ablative therapy 14.2% and radiotherapy 3.4%).

The median overall survival (OS) of all patients from the start of PRRT was 52 months (mo). Median OS according to radionuclide used: Y-90 24 mo, Lu-177 55 mo, both 64 mo; according to the grade of tumor: G1 87 mo, G2 55 mo, G3 28 mo, unknown 50 mo; and according to origin of primary tumors: pancreas 45 mo, small intestine 77 mo, unknown primary 55 mo, lung 36 mo. Median progression-free survival (PFS) measured from the last therapy cycle was 22 mo, comparable for pancreatic (23 mo) and small intestinal (25 mo) NETs.
Results of a German Multi-institutional Registry Study

A German multi-institutional registry study with prospective follow up in 450 patients indicates that PRRT is an effective therapy for patients with G1-2 neuroendocrine tumors, irrespective of previous therapies, with a survival advantage of several years compared to other therapies and only minor side effects. Median overall survival (OS) of all patients from the start of treatment was 59 months. Median progression-free survival (PFS) measured from last cycle of therapy accounted to 41 mo. Median PFS of pancreatic NET was 39 mo. Similar results were obtained for NET of unknown primary (median PFS: 38 mo) whereas NET of small bowel had a median PFS of 51 months. Side effects like °3-4 nephro- or hematotoxicity were observed in only 0.2% and 2% of patients respectively.

We also have treated patients with progressive metastases of NETs and with a single functional kidney (24 patients). None of these patients showed grade 3 or 4 nephrotoxicity. PRRT resulted in partial remission in 36% and stable disease in 36% of the patients, 28% had PD. In 2009, we have given fractionated low dose PRRT to 2 patients on hemodialysis (to the best of our knowledge, this was the first ever worldwide experience).

The Bad Berka neuroendocrine tumor center was the first also to use Y-90 DOTATATE, and in a large patient group, Lu-177 DOTATOC in progressive NETs, non-responsive to octreotide/interferon treatment or chemotherapy.

An important influence on the decision of the choice of radionuclide is the size of tumors. More commonly, patients present with tumors of various sizes and inhomogeneous distribution of somatostatin receptors. The use of a combination of radionuclides Lu-177 and Y-90 takes this heterogeneity into account. Sequential administration of Y-90 and Lu-177 labeled analogues also is similarly helpful for the treatment of larger tumors, followed by treatment of smaller metastases respectively in further treatment cycles. The BBNETC group pioneered the systematic use of Y-90 and Lu-177 DOTATATE (DUO PRRT) in sequence and concurrently, as well as the intra-arterial use of Y-90 DOTATATE and DOTATOC.

Lu-177 DOTATATE or Lu-177 DOTATOC is predominantly used for small metastases or in patients with impaired renal or haematological function. Long term follow-up of up to 9 years after DUO PRRT showed no significant grade 3 or grade 4 nephrotoxicity attributed to concurrent or sequential DUO PRRT. The median fall in
tubular extraction rate (TER) was lesser in patients undergoing DUO PRRT than in those undergoing PRRT with Lu-177 or Y-90 alone. The results of a study by Kunikowska et al also indicated that TANDEM PRRT (with Y-90/Lu-177 DOTATATE) provided longer overall survival than with a single radioisotope (Y-90 DOTATATE) and the safety of both methods was comparable.

**Conclusions**

PRRT lends a significant benefit in OS in metastasized and / or progressive G1-2 NETs as compared to other treatment modalities and regardless of previous therapy. Combination of Lu-177 and Y-90 (duo) based PRRT may be more effective than either radionuclide alone. Thus, in patients with progressive NETs, fractionated, personalized PRRT with lower doses of radioactivity given over a longer period of time (Bad Berka Protocol) is effective even in advanced cases and results in excellent therapeutic responses. Up to 10 cycles of PRRT, given over several years were tolerated very well by most patients. Severe haematological and/or renal toxicity can be avoided or reduced. Quality of life can be significantly improved. Though cure is rarely possible, excellent palliation with significant improvement of symptoms can be achieved by PRRT. In addition, neoadjuvant PRRT could be administered in cases of inoperable NET so as to render the tumor operable by inducing radiation induced necrosis.

However, PRRT should only be performed at specialized centers as NET patients need highly individualized interdisciplinary treatment and long term care. Use of intra-arterial PRRT (> 100 treatments already performed up to now) is more effective for selectively targeting liver metastases and large, inoperable primary tumors. PRRT can be effectively combined with transarterial chemoembolization (TACE), radiofrequency ablation (RFA), chemotherapy (e.g. using Capecitabine, Temozolomide or Doxorubicin), kinase inhibitors (e.g. Everolimus).

The concept of THERANOSTICS has now been translated to other malignancies (e.g. prostate cancer using PSMA as ligand). Current state and future perspectives of this fascinating precision treatment of malignancies will be discussed.
References


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