1c

The role of PET and PET/CT for the molecular diagnosis of neuroendocrine tumours and clinical experience with Peptide Receptor Radionuclide Therapy (PRRT) using radiolabelled somatostatin analogs in over 200 patients.

R.P. Baum (Bad Berka)

Gallium-68 labelled somatostatin analogs (e.g., DOTA-NOC or DOTA-TOC) can be used for the specific detection of neuroendocrine tumors (NET) and receptor positive metastases with high sensitivity (> 95–100 %) and very high specificity, allowing a whole-body diagnosis by PET/CT in one diagnostic procedure. Even very small primary tumors and metastases (< 5 mm), which are difficult to diagnose by CT, MRI or sonography, can be detected if the receptor density is high. If there is strong suspicion of a GEP tumor, or if a NET has been proven by immunohistochemistry, receptor PET/CT (or SMS scintigraphy) should be the first diagnostic procedure for staging (before CT and MRI). Further indications are the follow-up after surgery and the diagnosis of recurrences in case of increasing specific tumour markers; the evaluation of therapy response control after chemotherapy or biological therapy; and the differential diagnosis of neuroendocrine tumour vs. non-endocrine tumour in case of a space occupying mass, if a final diagnosis can not be obtained by biopsy or operation. Finally, there is an essential role for receptor PET/CT and somatostatin receptor scintigraphy in the pretherapeutic evaluation (receptor density, pretherapeutic dosimetry, e.g. using Yttrium-86 labelled analogs) before peptide receptor radionuclide therapy and in the follow-up after treatment.

The radiolabelling of specific peptides, which bind to somatostatin receptors on neuroendocrine tumours, with beta emitters like Yttrium-90 or Lutetium-177 enables an internal radionuclide therapy at low radiation risk for normal tissues (there is only a significant radiation burden to the kidneys and too a much lesser extent to the bone marrow) which can be repeatedly performed. Especially those patients with slowly growing hepatic and extrahepatic metastases (which are a poor target for chemotherapy) and those, where all surgical options have been used, are good candidates for peptide receptor radiotherapy (PRRT). Also patients who are progressing under octreotide therapy or under combined biotherapy and those with persisting symptoms (diarrhoea, flushs) despite high dose hormonal therapy are suitable for PRRT. The results obtained in several European centers (e.g. Basel, Rotterdam, Milano, Bad Berka) as well as of multicenter trials, show a promising tumour response rate and a significant improvement of clinical symptoms after PRRT. In Bad Berka, more than 200 patients with neuroendocrine tumours have been treated during the last 3 years, applying over 450 administrations (mean activity per cycle 3.5 GBq Y-90, or 5 GBq Lu-177, time between cycles 3 to 6 months). Also intra-arterial injections were given, mainly in patients with large inoperable primary tumours. Before and during each treatment amino acid solutions, containing arginine and lysine were infused IV over 3.5 hours to reduce kidney dose. All pts were selected based on high SSTR expression (immunohistology, SSTR scintigraphy, Ga-68 receptor PET/CT. Before each new cycle, restaging was performed by CT/MRI, PET (FDG, DOTA-NOC, fluoride), SSTR scintigraphy and tumour markers (CgA, serotonin). Renal function was serially determined (Tc-99m MAG3 scintigraphy and DTPA clearance). Whole-body and tumor dosimetry was performed under treatment by serial scintigraphy.

Bone marrow toxicity WHO grade 2 or 3 occurred in less than 15 % of the administrations. Thrombocytopenia/anemia were seen mainly in patients pretreated with chemotherapy and in those with widespread skeletal metastases. In none of the patients with normal kidney function before treatment, renal insuffiency developed, in most patients serum creatinine and TER/DTPA clearance did not change

significantly. Some pts had complete remission, about one third had partial remission (PR), and half of the pts had stable disease (SD), whereas about 10 % had PD. Objective tumor responses (including improvement of symptoms) were seen in 85 % of the pts.

Summary and conclusions:

Diagnosis: Receptor PET/CT using Ga-68-labelled DOTA-NOC (up to now 450 studies) enables the molecular imaging of neuroendocrine tumours with very high diagnostic sensitivity and specificity (current gold standard for imaging).

Therapy: Peptide Receptor Radiotherapy (e.g. using Y-90 or Lu-177 labelled DOTA-TATE) is well tolerated with relatively low toxicity and shows significant therapeutic efficacy in patients with progressive neuroendocrine tumours even after octreotide treatment or chemotherapy.

References

1. Baum RP, Hofmann M. Nuklearmedizinische Diagnostik neuroendokriner Tumoren. Onkologe 2004;10:598-610.
2. Baum RP, Söldner J, Schmücking M, Niesen A. Peptidrezeptorvermittelte Radiotherapie (PRRT) neuroendokriner Tumoren. Onkologe 2004;10:1098-1110.
3. Bombardieri E, Aktolun C, Baum RP, et al. 111In-pentetreotide scintigraphy: procedure guidelines for tumor imaging. Eur J Nucl Med Mol Imaging 2003;30:BP140-147.
4. Adams S, Baum RP, Hertel A, Schumm-Draeger PM, Usadel KH, Hör G. Comparison of metabolic and receptor imaging in recurrent medullary thyroid carcinoma with histopathological findings. Eur J Nucl Med 1998;25:1277-1283.
5. Kwekkeboom DJ, Mueller-Brand J, Paganelli G et al. Overview of results of peptide receptor radionuclide therapy with 3 Radiolabeled Somatostatin Analogs. J Nucl Med 2005;46:62S-66S