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Radionuclide therapy of GEP tumours

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The discovery of somatostatin receptor (SSTR) subtypes on various neuroendocrine tumors has stimulated the development of SST-analog-based scintigraphy and radionuclide therapy. SSTR scintigraphy has improved the ability to diagnose, detect, stage and review the response to therapy in patients with GEP tumors. In the management of SSTR positive tumor patients these new radiopeptides have developed as new potential treatment option, but their exact role still remains to be determined. The best SSTR radioligand should be carefully investigated by preceding diagnostic dosimetry because of the different binding behavior to SSTR subtypes expressed on the surface of GEP tumor cells. At present, many treatment protocols exist with different SST analogs as well as different study design. Side effects, kidney protection with amino acids and dose of radiopeptide for successful treatment are still under debate, and long-term results and survival rates are reported only for a few number of centers.

This presentation will review radionuclide treatment strategies and results in GEP tumor patients using either ^{90}Y -DOTA-Tyr³-octreotide, ^{177}Lu -DOTA-Tyr³-octreotate or ^{90}Y -DOTA-lanreotide / ^{177}Lu -DOTA-lanreotide. At the University of Innsbruck, initial staging and/or restaging of GEP tumor patients is usually performed with the PET tracer ^{68}Ga -DOTA-Tyr³-octreotide. In order to calculate tumor and normal organ doses, dosimetry is done following injection of ^{111}In -DOTA-Tyr³-octreotide, always preceding radionuclide treatment with either ^{90}Y -DOTA-Tyr³-octreotide or ^{177}Lu -DOTA-Tyr³-octreotate. Only if octreotide-based PET scans are negative, lanreotide-based PET scanning is performed for tumor evaluation. If the ^{68}Ga -DOTA-lanreotide PET scan indicates suitable tumor uptake, dosimetry is performed with the ^{111}In -DOTA-lanreotide compound for tumor and normal organ doses prior to therapy with a lanreotide-based radiotherapeutic.

The biodistribution of ^{111}In - ^{90}Y -DOTA-Tyr³-octreotide differs from that of ^{111}In - ^{90}Y -DOTA-lanreotide in terms of higher liver and kidney, and less bone marrow uptake. The MAURITIUS (Multicenter Analysis of a Universal Receptor Imaging and Treatment Initiative, a eUropean Study) trial was initiated in 1997 at the University of Vienna, and several centers throughout Europe have treated tumor patients with ^{90}Y -DOTA-lanreotide. Data reported are based on results from studies of Cesena, London, Milano, Innsbruck and Vienna (1). At most centers, comparative scintigraphy with ^{111}In -DTPA-D-Phe¹-octreotide or ^{111}In -DOTA-Tyr³-octreotide was performed for tumor evaluation. Dosimetric studies were performed to predict individual tumor doses and doses for the critical organs. A MAURITIUS update was performed in a total of 235 patients with neuroendocrine tumors, thymoma, thyroid cancer, brain tumors, lymphoma, intestinal adenocarcinoma or other rare tumors. Patients received up to 8.5 GBq of ^{90}Y -DOTA-lanreotide in up to 7 treatment applications. The therapeutic agent ^{90}Y -DOTA-lanreotide was given either intravenously (121 patients), intraarterially (21 patients), or by local intratumoral injection (93 patients). Patients were at a stage of progressive disease when entering treatment with ^{90}Y -DOTA-lanreotide. During the follow-up period, disease was evaluated by repeated scintigraphy and computed tomography/magnetic resonance imaging, documenting the response to therapy in terms of stable tumor disease, progressive disease, partial remission or complete remission, as well as by documenting the time of progression of disease and quality-of-life parameters. Overall results indicate that beneficial effects can be suspected from therapy with ^{90}Y -DOTA-lanreotide. A 5 years follow-up period indicated that 37 % (40/109) of the patients treated with ^{90}Y -DOTA-lanreotide had stable disease and 18 % (18/109) partial remission of tumor lesions.

Objective response of quality of life measurements was documented in 10-20 % of patients, and subjective response was found in 30-50 % of patients.

Kwekkeboom et al. (2) recently reported in 131 patients with GEP tumors very promising results with ^{177}Lu -DOTA-Tyr³-octreotate (cumulative dose of 22.2 – 29.6 GBq). Complete remissions were seen in 2 % of patients, partial remission in 32 patients (26 %), minor response in 24 patients (19 %), stable disease in 44 patients (35 %) and progressive disease in 22 patients (18 %). In this report, median time to progression in 103 patients who either had stable disease or tumor regression was more than 36 months.

Higher remission rates were positively correlated with high uptake on pretherapeutic SSTR imaging and limited number of liver metastases.

Results with ^{90}Y -DOTA-Tyr³-octreotide are also very promising, however, various centers are using different doses and dose regimes (3-5). This radiotherapeutic is also very promising with, generally spoken, about 50 % stabilisation rates of the disease and 25 % minor or partial remission rates in patients with GEP tumors. World-wide, at least 800 patients have been treated with this radiotherapeutic over the last 8-10 years, about 100 patients in Austria over the last 5 years.

The combination therapy of ^{90}Y -DOTA-Tyr³-octreotide with ^{177}Lu -DOTA-Tyr³-octreotate and/or ^{177}Lu -DOTA-lanreotide with ^{90}Y -DOTA-lanreotide is also discussed.

In cancer patients sources of satisfaction and self-esteem can be compromised. Fearfulness, therapeutic side effects, and the possibility of treatment failure and death are always present. These aspects may affect health-related quality of life, which includes both physical and psychological components. Thus, improvement in quality of life is an important goal of oncological treatment beyond and perhaps independent of the curative one. Marked improvement in quality of life parameters, despite minor effects on tumor shrinkage, have been reported in several studies using objective criteria. Objective response of quality of life measurements was documented in 10-20 % of patients, and subjective response was found in 30-50 % of patients.

In summary, the choice of radiopharmaceutical will depend upon resource facilities and logistics of each nuclear medicine department. The overall results of receptor therapy with radiolabeled SST analogs indicate that these molecular therapy has its place in patients with SSTR-positive tumors for size reduction and improvement of quality-of-life. Serious side effects are rare, especially in combination with amino acids for kidney protection. Patients should always be evaluated by preceding SSTR scanning and dosimetry using respective octreotide or lanreotide analogs. At the University of Innsbruck the current evaluation procedure includes a ^{68}Ga -DOTA-Tyr³-octreotide / lanreotide PET Scan, followed by dosimetry with the indium-labeled analog. These procedure is repeated during therapy with the therapeutic yttrium or lutetium-analog.

References

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