

Differential Therapy for Neuroendocrine Tumors

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Neuroendocrine tumors (NETs) encompass a very heterogeneous group of malignomas and can vary very dramatically in their clinical progression. The spectrum ranges from more benign, well-differentiated neuroendocrine tumors without invasive growth or metastases to rapidly proliferating, minimally differentiated neuroendocrine carcinoma that behaves biologically in a manner similar to small cell lung carcinoma. Treatment of NETs is oriented toward tumor stage, degree of differentiation, origin, functional activity, and receptor density.

Ideally, NETs are completely removed surgically at the beginning of the disease and, as a result, cured. However, this only happens regularly with NETs of the appendix. Most of these tumors are detected by chance within the course of an appendectomy and only seldom do they require second resection for oncological factors or systemic treatment at all. NETs of the rectum are frequently removed completely through polypectomy; however, it is to be observed that upon infiltration of the submucosa, lymph node metastases are often already present. The current situation regarding surgery for NETs will be presented in this issue by M. Hommann and D. Kämmerer. The disease in terms of NETs of other origin is in contrast usually generalized at time of diagnosis and distant metastases are most frequently present (most often in the liver or bone). As a result, conservative treatment must usually limit itself to a palliative approach which, however, requires a graduated and differentiated course of action with consideration given to the situation of the patient. The extraordinary variability of tumor growth over the course of the disease

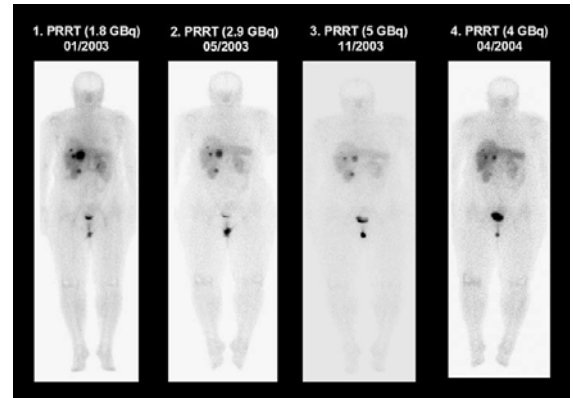


Figure 1

Radioreceptor therapy in a 43 year-old female patient with an expanded hepatic metastasized glucagonoma (primary tumor located in the pancreatic cauda) and progression prior to PRRT: extensive regression of the liver metastases after four treatments with Y-90 DOTATATE. The patient was professionally active without restriction during the entire time of treatment and today, five years after the first therapy and 31 months after a total of five treatments, is still in remission (normal renal function, GFR 94%, and hemogram showing no pathological findings) and without clinical symptoms.

can mean that the tumors remain stable for many years, even during spontaneous progression, very seldom show (partial) remissions, only to proliferate again. These observations led some practitioners to wait 3-6 months at the beginning of the disease during the spontaneous progression and, only once progression had been determined, to intervene therapeutically. According to our experiences and the recommendations of other large centers, specific therapy should begin as early as possible as long as the tumor burden is still minimal because with each progression of the disease fewer treatment modalities are available. In principle, every therapist (and NET patient also) should be aware that the progression of the disease can stretch out over years and decades, often with few restrictions in capacity, and that often multiple different

treatment modalities are required in stages to limit tumor burden. This approach requires a high degree of adaptation to individual needs on the one hand, and extensive experience on the part of the attending physicians on the other (coordination of the procedure through interdisciplinary tumor consultation) since another course of action is required here than in the usual “standardized” approach, for instance, for oncological treatment of common solid tumors.

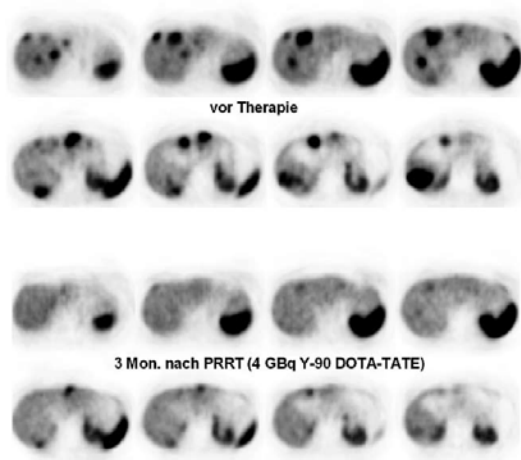


Figure 2
⁶⁸Ga-DOTA-NOC receptor PET/CT (imaging only of the transversal PET images): partial remission of liver metastases of a non-functional NET of the pancreas following one-time RRT with 4 GBq Y-90 DOTA-TATE.

The expression of somatostatin receptors by neuroendocrine tumors forms the basis for biotherapy with somatostatin analogs. Somatostatin receptors (SSR) are expressed in five isoforms of NETs and other tumors (SSR1-SSR5). These receptors are G-protein coupled and effect a reduction of secondary transmitters, such as cAMP or calcium, in the cell and, as a result, a decrease in secretion. Presently, two somatostatin analogs are available: octreotide (Sandostatin®) and lanreotide (Somatoline®). The somatostatin analogs are approved for treatment of functional NETs to reduce secretion of hormones and messenger substances and lead in this case to a decrease in complaints, such as flushing or diarrhea, in the majority of patients. In addition, the somatostatin analogs are

frequently used to control tumor growth. In uncontrolled studies an efficacy in terms of this is described; however, the results of a double-blinded, randomized, prospective study are not yet available. It can be expected that a (small) portion of patients also profit anti-proliferatively from somatostatin analogs. The currently available somatostatin analogs bind primarily to the somatostatin receptor 2 (SSR2) and less strongly to SSR5 and SSR3. A somatostatin analog undergoing testing, SOM230 (pasireotide), binds to all five SSRs and as a result can induce a stronger effect on functional syndromes than the conventional somatostatin analogs. Testing of the anti-proliferative activity of SOM230 in the case of NETs has yet to occur. Combination of somatostatin analogs with interferon is not of additional value to most patients so that this combination is increasingly used less often. Prior to application of somatostatin analogs for anti-proliferative purposes, radiological detection of somatostatin receptors should take place; in terms of functional syndromes, a therapeutic attempt is justified in any case.

Chemotherapy plays a critical role with the rapidly proliferating, undifferentiated neuroendocrine carcinomas (WHO class III or G3). Here, mainly combinations consisting of a platinum preparation (cisplatin or recently increasingly carboplatin) with Etoposide are applied. These tumors generally respond well to the initial chemotherapy, but recidivate quickly and frequently, and are treated in second-line therapy the same as small cell lung carcinomas. Of the well-differentiated neuroendocrine carcinomas, only the NETs of the foregut (lungs, stomach, duodenum, pancreas) respond to polychemotherapy. For this purpose, combinations based on streptozotocin with doxorubicin or 5-fluorouracil are used. Response to chemotherapy in terms of these tumors (stable disease in the case of previously documented progression or partial remission) is approximately 50%. Rectal carcinomas are also limitedly sensitive to chemotherapy, while the common small

bowel NETs only show a response rate of less than 20% which is why chemotherapy is not recommended for these tumor entities.

The expression of SSRs by the NETs is also the basis for peptide receptor radionuclide therapy (PRRT), or in short radioreceptor therapy. In this procedure, a radioactive therapeutic nuclide is bound by a chelator (= DOTA) to a somatostatin analog (octreotate=DOTA-TATE or tyrosine-octreotide=DOTA-TOC). Depending on tumor size/metastases, ⁹⁰Yttrium (beta emitter with a range of approximately 12 mm in tissue) or ¹⁷⁷Lutetium (beta emitter with a smaller range of approximately 2 mm) is used as therapeutic nuclide. ⁹⁰Yttrium is preferred for larger tumors and ¹⁷⁷Lutetium is often applied in the case of smaller tumors. Both radiopharmaceuticals can also be successfully applied sequentially, a process that was first employed at our clinic. Due to the highest affinity to SSR2, DOTA-TATE currently appears to be the optimal peptide for therapy (best target-non-target ratio and highest tumor uptake). Commercial introduction of ⁹⁰Yttrium-DOTA-TOC is planned; the first studies for drug registration are planned Europe-wide for 2008. Because of potential renal and hematological toxicity, it is important to precisely define the patient groups who will most probably profit from therapy. The amount of the radioactivity applied here ("therapeutic dose") depends on somatostatin receptor expression, tumor burden, kidney function, and hematological status. The toxicity of PRRT can be reduced and to a large extent avoided through multiple applications of lower amounts of radioactivity (concept behind "Bad Berkaer PRRT").

The clinical efficacy of radioreceptor therapy could be demonstrated in large studies. Our own results for more than 500 treated NET patients (1,500 treatments) over the last seven years show a response rate of clearly over 80% (combination of complete and partial remission, as well as stable disease with previous progression). Primary progress during PRRT appears in

less than 15% of patients and is connected with a very poor prognosis. If patients respond to treatment, then the length of time until the next progression is on average 40 months and survival on average more than 48 months. Pancreatic NETs – in particular glucagonomas ((Figure 1) and gastrinomas, as well as midgut NETs ("carcinoids") – respond best to PRRT, but so do other neuroendocrine tumor entities with a high SS receptor density, such as paragangliomas /pheochromocytomas, aesthesioneuroblastomas, invasive glomus tumors, etc. Interestingly, the efficacy of radioreceptor therapy does not clearly depend on the proliferation rate if there is high SS receptor expression. Consequently, PRRT currently poses the most efficacious palliative tumor therapy for eligible patients. The potential hematogenic and nephrogenic toxicity of PRRT must be taken into account, above all in terms of patients who have already received chemotherapy. A clinically meaningful decrease of renal function can be avoided as far as possible through suitable measures (application of basic amino acids for the purpose of nephroprotection) which requires constant monitoring following treatment.

Analogous to treatment of chronic myelogenous leukemia or gastrointestinal stroma tumors with imatinib, targeted treatment of NETs with molecularly defined substances would be a desirable option. Demonstration of an activation of mTOR kinase and VEGF receptors in the NETs provides the basis for therapy with RAD001 as mTOR inhibitor and sunitinib as VEGF inhibitor which can also inhibit other potentially activated tyrosine kinases. Successfully conducted phase II studies are available for both substances. Fortunately, at present many large randomized, prospective, placebo-controlled studies are being conducted internationally on patients with midgut NETs (RAD001; Radiant-2) and pancreatic NETs (RAD001; Radiant-3 study, Sutent NET study). These studies are mainly suitable for patients who have already received multiple treatments since the substances undergoing testing have a low

profile regarding side-effects. Should these studies demonstrate the efficacy of the test substances, the limited arsenal for treating NETs would be considerably expanded.

Well-elaborated European guidelines offering an overview of the various therapy modalities and treatment of the individual NETs exist for treating (and diagnosing) NETs. These guidelines can be downloaded at <http://www.neuroendocrine.net/>. Further information on therapy for neuroendocrine tumors is also available on our website at <http://www.rhoen-klinikum-ag.com/rka/cms/zbb/deu/3310.html>.

Literature available from the authors upon request

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