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PRRT of neuroendocrine tumours using [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate: long-term experience and future perspectives

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General: There are few treatment options for patients with metastasized or inoperable endocrine gastro-entero-pancreatic (GEP) tumors. Treatment with somatostatin analogues or interferon-alpha can result in symptomatic control of the disease in the majority of patients, but anti-proliferative effects are rare. Chemotherapy is usually reserved for a minority of patients who have rapid tumor growth. Also, chemotherapy results in tumor size reduction in a relatively low percentage of cases (typically less than 20%) and time to tumor progression is usually less than 18 months. For other, local, therapies like radiofrequency ablation (RFA) or (chemo)embolisation of liver metastases response rates of in between 25-85% have been reported in relatively small patient groups. Importantly, this type of therapy is limited to only patients having most of their tumorload in the liver, and localization and size of the metastases may preclude such treatment. Treatment with the radiolabelled somatostatin analogue [^{177}Lu-DOTA^{0},Tyr^{3}] octreotate is a relatively new and challenging treatment option for patients with somatostatin receptor positive tumors.

Treatment: From January 2000 to July 2006 1968 administrations in 562 patients were performed. Patients with somatostatin receptor positive tumors were treated up to a cumulative dose of 600-800 mCi (22.2-29.6 GBq).

Toxicity: Acute toxicities in 504 patients receiving 1772 treatments according to protocol were: nausea (25% of administrations), vomiting (10%) and abdominal discomfort or pain (10%). Any grade 3 or 4 haematological toxicity occurred after 3.6% of administrations. Possible or probable treatment-related serious adverse events were temporary liver toxicity in 2 patients, and myelodysplastic syndrome in 3 patients. In 2 out of 205 Dutch patients who had at least 18 months of follow-up, a possible treatment-related decrease of more than 25% in creatinine clearance was found.

Efficacy: 2% of patients had complete tumor remission (CR), 28% had partial remission (PR), and 17% had minor remission (MR), 35% had stable disease (SD), and 20% had progressive disaese (PD). Median time to progression in patients having CR, PR, MR, or SD was 40 months. Median overall survival and disease related survival were 46 months and >48 months, respectively.

Discussion and outlook: Treatment with [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate results in tumor remission in a high percentage of patients with GEP tumors. Serious side-effects are rare. The median time to progression and survival compare very favorably to the limited alternative treatment modalities. A new initiative to improve the results is a randomized controlled study comparing treatment with [^{177}Lu-DOTA^{0},Tyr^{3}] octreotate only to treatment with the chemotherapeutic agent capecitabine and [^{177}Lu-DOTA^{0},Tyr^{3}] octreotate. Combinations with other agents and also combinations of somatostatin analogues labelled with different radionuclides as well as strategies to upregulate the receptor expression are other options that can and should be tested in future randomised controlled trials.

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