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8

Peptide receptor radionuclide therapy of neuroendocrine tumours

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In the past decades, the number of neuroendocrine tumours that are detected is increasing. A relative new and promising therapy for patients with metastasised or inoperable disease is peptide receptor radionuclide therapy (PRRT). This therapy involves an infusion of somatostatin analogues linked to radionuclides like Yttrium-90 or Lutetium-177. Objective response rates are reported in 15–35%. Response rates may vary between type of tumour and radionuclide. Besides the objective response rate, overall survival and progression free survival increase significantly. Also, the quality of life improves as well. Serious side-affects are rare. PRRT is usually well tolerated, also in patients with extensive metastasised disease. Recent studies combined PRRT with other types of therapies. Unfortunately no randomised trials comparing these strategies are available. In the future, more research is needed to evaluate the best therapy combinations or sequence of therapies.

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Introduction

Neuroendocrine tumours (NETs) are a heterogeneous group of tumours. These tumours can induce a number of symptoms (e.g. carcinoid syndrome) or can be asymptomatic for a long time. Unfortunately, more than 50% of the patients have metastatic disease at time of presentation. When NETs are metastasised, no curative treatment option is available. Surgery, the only therapeutic option with a curative intent, is reserved for limited disease (no or few metastases). For the large group of patients with metastatic disease different types of treatment were developed in the last decades. One of the most promising is Peptide Receptor Radionuclide Therapy (PRRT). This therapy is based on the fact that the majority of neuroendocrine tumours express the somatostatin receptor (SSTR) on their surface. This receptor is the target for somatostatin analogues (SSA), which is an effective first line treatment for especially midgut NETs in terms of time to progression [1]. In the nineties of the past century, the first research groups started with PRRT using SSA labelled with Indium-111 (^{111}In-DTPA-Octreotide) [2,3]. This radiopharmaceutical, which emits y-rays, can be used for imaging of neuroendocrine tumours. It also emits Auger electrons, which can be used for therapy. The results of PRRT with ^{111}In-DTPA-Octreotide were reasonable, however the number of patients with a complete or partial response (CR, PR) was low. In the following years, radiolabelled somatostatin analogue therapy became more advanced, with the introduction of PRRT with analogues labelled with the β-emitting radionuclides Lutetium-177 or Yttrium-90. In general, PRRT with radiolabelled somatostatin analogues is used mostly for NETs, but can also be used for other somatostatin receptor positive disease such as paragangliomas, meningiomas and iodine refractory thyroid cancer [4–6].

Efficacy

In vivo stability of the radiolabeled peptide is an important factor that contributes to its success. For the Yttrium-90 and Lutetium-177 based PRRT, the stable binding of the somatostatin analogues linked to the radionuclide is established via the chelator 1,4,7,10-tetraazacyclotetradecane-1,4,7,10-tetraacetic acid (DOTA). With the use of DOTA, these radionuclides can bind to different somatostatin analogues, such as octreotide or octreotate.

The results of several phase 1/2 studies have been published in the last decade. Different somatostatin analogues with different affinity profiles to the five known subtypes were labelled with Yttrium-90 or Lutetium-177. Although in most studies Yttrium-90 is linked to the analogue [Tyr3] octreotide and Lutetium-177 to the analogue [Tyr3]octreotate, different combinations of analogues and chelators have also been tested.

Considering the radionuclides used, there are some differences in physical properties between Yttrium-90 and Lutetium-177. The half-life of Lutetium-177 is 6.7 days versus 2.7 days for Yttrium-90. Furthermore, the tissue penetration of Yttrium-90 is 12 mm and of Lutetium-177 is 2 mm. This longer tissue penetration of Yttrium-90 is especially beneficial in tumours with a heterogeneous receptor expression. The shorter tissue penetration of Lutetium-177 makes this radionuclide probably more suitable to treat also smaller tumours [7]. Besides β-emission, Lutetium-177 also emits y-rays that can be used for imaging in the days after therapy. Therefore, these images can be used to verify the targeted delivery of the radiopharmaceutical and to calculate absorbed dose in organs/tissues and SSTR positive tumours.

Yttrium-90

One of the first studies with PRRT other than ^{111}In-DTPA-Octreotide was published in 2001 by Waldherr et al. [8]. Patients with gastroenteropancreatic (GEP-NETs) and bronchial NETs were included and treated with [^{90}Y-DOTA^{0},Tyr^{3}]Octreotide (^{90}Y-DOTATOC). The overall response (complete and partial remission) was 24%. For pancreatic NETs the response was 36%. Since then numerous reports from several research groups involved in PRRT were published (Table 1). The number and type of SSRT positive tumours that were treated varied between the studies. Therefore, interstudy comparison of the outcome reported within these studies remains difficult. The largest group of patients studied [9] (1109 patients) showed a morphological response in 34% of patients. However, it was a mixed group