

Internal irradiation of neuroendocrine tumors with Yttrium-90-DOTATOC, a radiolabeled somatostatin analogue

Patient information file

Ladies and Gentlemen

You are diagnosed with a neuroendocrine tumor and scheduled for one or two cycles of ^{90}Y -DOTATOC treatment at our institute.

What is a neuroendocrine tumor?

Every human has neuroendocrine cells. Neuroendocrine cells are widely spread over the whole body, but occur mainly in the bowel, in the pancreas and in the lungs. The job of neuroendocrine cells is the production of hormones (signal substances).

Probably years ago during the rebuilding process of a neuroendocrine cell (where a mother cell divides into daughter cells), an information translation failure happened. Now the new daughter cells do not know when to die, how many new cells to build and how to behave while coming in contact with normal cells. This leads to an overproduction of neuroendocrine cells which displace normal tissue. Luckily neuroendocrine cells normally grow slowly.

Neuroendocrine tumor cells often produce too many hormones which lead to several symptoms. These symptoms are called malignant carcinoid syndrome. Probably you know these symptoms as flushes, diarrhoea, alcoholic intolerance, wheezing or skin problems.

How does the Yttrium-90-DOTATOC-treatment works?

Neuroendocrine cells carry somatostatin receptors. No other tissue has them in such a high density. The peptide DOTATOC is the key to the somatostatin receptor. The DOTATOC has a high affinity to the somatostatin receptor and is linked to a therapeutic, β -emitting radioisotope. The radiation emitted from a radiolabeled peptide bound to a tumor cell kills the tumor and neighbouring cells. Yttrium-90-DOTATOC is injected intravenously and links to the tumor within a few minutes.

Is this therapy dangerous for me and will I experience any discomfort?

Normally the treatment is well tolerated. Beta-emitting particles radiate within a diameter of 5 mm. Therefore most of the radiation exists only in the tumor and does not interact with your body.

One of the few side effects is the kidney uptake of the radiopeptide. ^{90}Y -DOTATOC can damage the kidney. Therefore we block the kidney by infusing amino-acids. The infusion of amino-acids does not cause any adverse effects.

Despite the kidney blockade, you have a minimal risk of developing a renal insufficiency. In rare cases haemodialysis may be needed.

While injecting ^{90}Y -DOTATOC, 20% of patients may suffer from nausea. Nausea can last for only minutes or several days. The injection of ^{90}Y -DOTATOC is normally well tolerated. However, some patients may feel like they have a hangover for up to one week.

After the treatment, a slight decrease of white and red blood cell count, of thrombocytes and lymphocytes is likely to occur. Within 7 weeks, most parameters will return to normal. In case of widespread liver metastases, stenosis of the gall bladder duct might be an adverse effect of ^{90}Y -DOTATOC. This situation would be cleared up by implantation of a stent.

What will happen to me during my stay in Basel?

One therapy session lasts 3 - 4 days. Either we perform 2 - 3 treatments with only ^{90}Y -DOTATOC or a combination of treatments with ^{90}Y -DOTATOC and ^{177}Lu -DOTATOC in an interval of about 10 weeks. The dose we are going to inject is adjusted to your body size and weight.

Before starting the treatment you will speak with our treating Nuclear Medicine Physician. Afterwards, he will place an intravenous cannula. Before injection of ^{90}Y -DOTATOC chemistry panel and complete blood count will be measured. Then 250 ml of an aminoacid solution will be infused followed by the ^{90}Y -DOTATOC injection. After ^{90}Y -DOTATOC injection the rest of aminoacid solution will be infused over 4 hours. While you are staying the following 2 days at the ward, scintigraphic images will be obtained to check the distribution of the radio-pharmaceutical.

What can I expect after being treated with DOTATOC? What are the results of research?

The results of a recent study:

Patients and Methods

39 patients (mean age 55y) with progressive neuroendocrine gastro-enteropancreatic and bronchial tumors were included. The treatment consisted of 4 equal intravenous injections of a total of 7.4 GBq/m² ^{90}Y -DOTATOC, administered at intervals of 6 weeks. After each treatment cycle, a life quality assessment was performed.

Results

The objective response rate was 21%. For endocrine pancreatic tumor (13 pts) it was 38%. Complete remissions (CR) were found in 5% (2/39), partial remission (PR) in disease (SD) in 49% (19/39) and progressive disease (PD) in 13% (5/29). These responses have been maintained for up to a median of 6 months (median duration of follow up, range 2 months to 12 months). A significant reduction of clinical features could be assessed in 83% of patients with diarrhoea, in 46% of patients with flushes, in 63% of patients with wheezing and in 75% of patients with pellagra. The overall clinical response was 63%. Side effects were grad III/IV (NCIGC) lymphocytopenia in 23%, anaemia grad III in 3% and renal insufficiency grade II in 3%.

Conclusion

High dose targeted radiotherapy with 7.4 GBq ^{90}Y -DOTATOC/m² is a well tolerated treatment for neuroendocrine tumors. It has a remarkable objective response rate and very good palliative effects.

Literature

Cremonesi M, Ferrari M, Zoboli S, Chinol M, Stabin MG, Orsi F, Maecke HR et al. Biokinetics and dosimetry in patients administered with ^{111}In -Tyr³-octreotide: implications for internal radiotherapy with ^{90}Y -DOTATOC. *Eur J Nucl Med* 1999; 26;8:877-886.

Otte A, Jermann E, Béhé M., Goetze M, Bucher HC, Roser HW, Heppeler A, Mueller-Brand J, Maecke HR: DOTATOC: a powerful new tool for receptor mediated radionuclide therapy. *Eur J Nucl Med* 1997; 24:792-796.

Otte A, Mueller-Brand J, Dellas S, Nitzsche EU, Herrmann R, Maecke HR. Yttrium-90 labelled somatostatin-analogue for cancer treatment. *Lancet* 1998; 351:417-418.

Otte A, Herrmann R, Heppeler A, Behe M, Jermann E, Powell P, Maecke HR, Mueller-Brand J. Yttrium-90 DOTATOC: first clinical results. *Eur J Nucl Med* (1999) 26:1439-1447.

Waldherr C, Haldemann A, Maecke HR, Pless M, Müller-Brand J. Tumorantwort und klinische Effektivität in der rezeptorvermittelten metabolischen Radiotherapie neuroendokriner Tumoren mittels ^{90}Y -DOTATOC: Eine klinische Phase II Studie. *Nuklearmedizin* 2000; 39: A20: V60.

Waldherr C, Haldemann A, Maecke HR, Crazzolara A, Mueller-Brand J. Exceptional results in neuroendocrine-metastases-caused paraplegia treated with [90Y-DOTA]-D-Phe¹-Tyr³-octreotide (90Y-DOTATOC), a radiolabelled somatostatin analogue. *Clin Oncol (R Coll Radiol)*. 2000;12(2):121-3.

Waldherr C., Schumacher T., Maecke H.R., Nitzsche E.U., Müller-Brand J.. Radionuclide Therapy of Somatostatin-Receptor-Positive Tumours using [^{90}Y -DOTA]-D-Phe¹-Tyr³-octreotide (^{90}Y -DOTATOC): The Basel Experience. *Suisse du Cancer* 2001 (2): 65-68.

Waldherr C, Pless M, Maecke HR, Haldemann A, Mueller-Brand J. The clinical value of [90Y-DOTA]-D-Phe¹-Tyr³-octreotide (90Y-DOTATOC) in the treatment of neuroendocrine tumours: a clinical phase II study. *Ann Oncol*. 2001 Jul;12(7):941-5.

Paganelli G, Zoboli S, Cremonesi M, Bodei L, Ferrari M, Grana C, Bartolomei M, Orsi F, De Cicco C, Maecke HR, Chinol M, de Braud F. Receptor-mediated radiotherapy with 90Y-DOTA-D-Phe¹-Tyr³-octreotide. *Eur J Nucl Med*. 2001 Apr;28(4):426-34.

Waldherr C, Schumacher T, Pless M, Crazzolara A, Maecke HR, Nitzsche EU, Haldemann A, Mueller-Brand J. Radiopeptide transmitted internal irradiation of non-iodophil thyroid cancer and conventionally untreatable medullary thyroid cancer using 90Y-DOTATOC. *Nucl Med Commun*. 2001 Jun;22(6):673-8.

Waldherr C, Pless M, Maecke HR, Schumacher T, Crazzolara A, Nitzsche EU, Haldemann A, Mueller-Brand J.. Tumor response and clinical benefit in neuroendocrine tumors after 7.4 GBq ^{90}Y -DOTATOC. *JNM* 2002; May.

Imhof A, Brunner P, Marincek N, Briel M, Schindler C, Rasch H, Maecke HR, Rochlitz C, Müller-Brand J, Walter MA. Response, Survival, and Long-Term Toxicity After Therapy With the Radiolabeled Somatostatin Analogue 90Y-DOTATOC in Metastasized Neuroendocrine Cancers. *JCO* 2011 Jun 10;29(17):2416-23.

Marincek N, Radojewski P, Dumont RA, Brunner P, Mueller-Brand J, Maecke HR, Briel M, Walter MA. Somatostatin receptor-targeted radiopeptide therapy with 90Y-DOTATOC and ^{177}Lu -DOTATOC in progressive meningioma: long-term results of a phase II clinical trial. *J Nucl Med*. 2015 Feb;56(2):171-6

Legalities and costs

The treatment conforms to Swiss laws as set forth by both the national and cantonal authorities. The protocol concerning the therapy was accepted by the ethic commission of the canton Basel-Stadt. The expenses of the Swiss patients are covered by their health insurance. The majority of foreign health insurance schemes also cover the costs of the therapy. A guarantee for this however cannot be made by our institute. Please inform yourself about the services that are covered by your health insurance before the therapy is scheduled.

You have the right at any time to withdraw from the therapy without giving any reason.

Legal authority

Please give us your permission to perform this treatment named above with your subscription. That means that this treatment was sufficiently explained to you and all your questions were sufficiently answered.

I agree that any of my medical notes and data collection during the PRRT, may be used for anonymised scientific evaluation.

Basel, date....., subscription.....

Doctor's signature.....