Trial Description

Title

PET/CT imaging and dosimetry as predictive factors for treatment response of the 177Lu-DOTA-TATE therapy

Trial Acronym

DOTADOSE

URL of the trial

[---]*

Brief Summary in Lay Language

The aim of this study is to obtain new findings about the 177Lutetium-DOTA-TATE therapy, which is a recommended therapy option for patients with metastasized non-operable neuroendocrine tumors.

Everybody has neuroendocrine cells in body. Neuroendocrine cells are diffusely distributed in gastrointestinal tract, in lungs and pancreas, mainly. The function of these cells is the production of different messengers (hormones). The cells of the body regenerate themselves periodically by use of cell division. In Patients with a neuroendocrine tumor there was an error during the cell division. The new neuroendocrine cell has lost genetic information. The following cells have more cell divisions as normal and do not dy. Thus there is a cell growth and a displacement of normal tissue. Fortunately neuroendocrine tumors have a slow growth in comparison to other kinds of tumors. Neuroendocrine tumors produce too much hormones usually. The high level of hormones can lead to a symptomatic which is called carcinoid syndrome. Possible symptoms are for example flush, diarrhoea, alcohol intolerance, asthma and problems with the skin.

In Patients with metastasized non-operable neuroendocrine tumors there is a possible recommended therapy option the 177Lutetium-DOTA-TATE therapy. Neuroendocrine cells have a so-called somatostatin receptor on their external surface. If a hormone binds on a receptor, this hormone gives its information about the receptor to the cell. Neuroendocrine tumors have the special somatostatin receptor in enormous number, mostly. That means in a higher number than normal cells. The hormone somatostatin can be produced synthetically (name: DOTA-TATE). DOTA-TATE binds on the receptor on the tumor cells and be there for a few days. “DOTA-TATE” is bound to a radioactive particle (name: Lutetium-177), which ray the tumor cells. 177-Lutetium-DOTA-TATE is injected intravenous, that means about the vein, and is in a few minutes at the tumor, predominantly.

In preparation for the 177Lutetium-DOTA-TATE therapy there is an imaging modality necessary to proof an adequate number of required somatostatin receptors. This imaging modality is called 68Gallium-DOTA-TATE PET/CT (Gallium-68: radioactive particle, suitable just for imaging, not for therapy because of different radiation characteristics in comparison to 177-Lutetium; DOTA-TATE: synthetic produced somatostatin, which binds on the somatostatin receptor; PET/CT: positron emission tomography in combination with computed

tomography). If there is a good enhancement of 68Gallium-DOTA-TATE in the neuroendocrine tumors, it indicates a high number of somatostatin receptors on the external surface and thus the 177Lutetium-DOTA-TATE therapy can be recommended. In doing so the enhancement in the neuroendocrine tumors has to be higher than in the liver.

A further condition of therapy is an adequate kidney function. A part of 177Lutetium-DOTA-TATE is reabsorbed by the kidneys like amino acids. The kidneys have to be blocked for "DOTA-TATE" to avoid an impaired kidney function. For this the patients receive intravenous infusion of amino acids. This infusion is well tolerated and is not dangerous for the kidneys. Under this amino acid blockade there is no impaired kidney function observed until now. However, this therapy has a risk to lead to a massive impaired kidney function (up to kidney dialysis).

In therapy the patients receive the radiolabeled substance 177Lutetium-DOTA-TATE divided into four therapy cycles with a distance of ca. eight weeks between every therapy cycle. One therapy cycle takes three days.
During hospitalization, imaging modalities are made for therapy control, on the one hand a conventional scintigraphy and on the other hand a SPECT/CT (single photon emission computed tomography, in combination with computed tomography).
Subsequent to the therapy (ca. three months after the last therapy cycle) the patients receive a 68-Gallium-DOTA-TATE PET/CT for a therapy control.

Aims of this study are as followed:
Until now by the conventional scintigraphy there is the opportunity to evaluate the radiation dose of tumors and organs with an analysis program based on a planar evaluation of the radiation dose or 2D evaluation of the radiation dose.
By the SPECT/CT we have a new method (a new analysis program) for the dose evaluation available. This new method depends on 3D evaluation of the radiation dose. We would like to compare the evaluation of the tumor dose of the 3D evaluation of radiation dose with the 2D evaluation of radiation dose. Probably, the 3D evaluation of radiation dose is superior to the 2D evaluation of radiation dose.
Furthermore, we would like to evaluate the 68Gallium-DOTA-TATE PET/CT and the 3D evaluation of radiation dose as predictive factors for the 177Lutetium-DOAT-ATE therapy response. The standard is the therapy response 3 months after 177Lutetium-DOTA-TATE therapy of the tumors respectively. Thus we could obtain important information with regard to the effect of the 177Lutetium-DOTA-TATE therapy.
In addition, we would like to analyse the 68Gallium-DOTA-TATE PET/CT as predictive factor for the tumor radiation dose as well as for the kidney radiation dose under 177Lutetium-DOTA-TATE. With an improved estimation of the kidney radiation dose under therapy you could avoid a possible impairment of the kidneys as a massive side effect of the 177Lutetium-DOTA-TATE therapy maybe. With the help of this improved diagnostic it could be able to realise a better individualized therapy for patients.

Patients were only included in this study when they were examined with 68Gallium-DOTA-TATE PET/CT in the department of nuclear medicine and after that had a 177Lutetium-DOTA-TATE therapy.
The examination and therapy of the patients depends on the clinical standards of the department of nuclear medicine. There are no additional interventions therefore there are no additional risks for the patients.
A deviation of the usual arrangements is only an advanced data acquisition and

data evaluation after the therapy.
The data are stored in the patient chart in a room with limited access authorization. The respective electronic data are saved by access authorization, too. The patients give their informed consent to the advanced data acquisition and evaluation under adherence to data protection.

Brief Summary in Scientific Language

The European Neuroendocrine Tumor Society (ENETS) recommended in their guidelines the treatment of metastasized non-operable tumors with the radiolabeled somatostatin analog 90Y-DOTATOC or 177Lu-DOTATATE (Eriksson et al. Neuroendocrinology 2008; 87:8-19).
The 90Y-DOTATOC and 177Lu-DOTATATE therapy is a receptor-mediated systemic radionuclide therapy. It is an effective therapy in most cases of neuroendocrine tumors, because these tumors overexpress the somatostatin receptor subtyp2 (sst2), mostly (Kwekkeboom et al. J Nucl Med 2005; 46:62S-66S).
In preparation for the 90Y-DOTATOC or 177Lu-DOTATATE therapy, until recently, there was a somatostatin receptor scintigraphy and “single photon emission computed tomography” (SPECT).
With these imaging modalities you were able to find out the evidence of the expression of the target receptors before therapy. If the tumor enhancement was higher than the liver enhancement, that was the indication for the 90Y-DOTATOC or 177Lu-DOTATATE therapy.
Meanwhile, the somatostatin receptor scintigraphy and SPECT have been replaced by the somatostatin receptor PET/CT (positron emission tomography in combination with computed tomography). Studies have shown that the somatostatin receptor PET/CT, for example with 68Ga-DOTATATE, shows a higher sensitivity as compared to somatostatin receptor scintigraphy and SPECT (Srirajaskanthan et al.J Nucl Med 2010;51:875-882). Furthermore with the new method you are able to quantify the tumor enhancement easily. For this reason, the new method has not only a higher sensitivity but also the potential to estimate the therapy response in the sense of a predictive imaging modality.
Furthermore we have a new method for the dose evaluation of tumors and organs available. This new method depends on 3D dosimetry (voxel-based dosimetry) and is superior to the planar dosimetry or 2D dosimetry, probably. Therefore, you are able to estimate the therapy response with the 3D dosimetry better than with the 2D dosimetry.

In this study, we would like to evaluate the 68Ga-DOTATATE PET/CT and the 3D dosimetry as predictive factors for the 177Lu-DOATATE therapy response. Furthermore we would like to compare the evaluation of the tumor dose with the 3D- and 2D dosimetry respectively in the same patient. The standard is the therapy response 3 months after 177Lu-DOTATATE therapy of the tumors respectively.
With the help of this improved predictive diagnostic it could be able to realise a better individualized therapy.

In this monocentric, retrospektiven study there were no additional interventions. Patients were only included in the study when they were examined with 68Ga-DOTATATE PET/CT in the department of nuclear medicine and after that had a 177Lu-DOTATATE therapy. The examination and therapy of the patients depends on the clinical SOPs (standard operating procedures) of the department of nuclear medicine.
A deviation of the usual arrangements is only an advanced data acquisition and evaluation. The data are stored in the patient chart in a room with limited access authorization. The respective electronic data are saved by access authorization,

too. There are no additional interventions, therefore there are no additional risks for the patients. The patients give their informed consent to the advanced data acquisition and evaluation under adherence to data protection in two forms (patient informed consent PET/CT; informed consent 177Lu-DOTATATE therapy).

Organizational Data

- DRKS-ID: **DRKS00004376**
- Date of Registration in DRKS: **2012/09/20**
- Date of Registration in Partner Registry or other Primary Registry: **[---]***
- Investigator Sponsored/Initiated Trial (IST/IIT): **yes**
- Ethics Approval/Approval of the Ethics Committee: **Approved**
- (leading) Ethics Committee Nr.: **355/12 , Ethik-Kommission der Albert-Ludwigs-Universität Freiburg**

Secondary IDs

Health condition or Problem studied

- ICD10: **C75.9 - Malignant neoplasm: Endocrine gland, unspecified**

Interventions/Observational Groups

- Arm 1: **Observation Group:**

  From patients (subject group), which have metastasized non-operable neuroendocrine tumors and therefore got a 177Lu-DOTA-TATE therapy, we evaluate the dosimetric data of the therapy retrospective; non-interventional study.

Characteristics

- Study Type: **Non-interventional**
- Study Type Non-Interventional: **Observational study**
- Allocation: **Single arm study**
- Blinding: **[---]***
- Who is blinded: **[---]***
- Control: **Uncontrolled/Single arm**

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Who is blinded: **[---]***

Control: **Uncontrolled/Single arm**

- Purpose: **Prognosis**
- Assignment: **Single (group)**
- Phase: **N/A**
- Off-label use (Zulassungsüberschreitende Anwendung eines Arzneimittels): **[---]***

Primary Outcome

triple phase CT scan; decrease in lesion-volume [ml]

Secondary Outcome

SUVmax [g/ml], tumor doses [Gy/GBq], kidney doses [Gy/GBq], correlation between conventional dosimetry and voxel-based dosimetry

Countries of recruitment

- DE **Germany**

Locations of Recruitment

- University Medical Center **Universitätsklinikum Freiburg, Freiburg im Breisgau**

Recruitment

- Planned/Actual: **Actual**
- (Anticipated or Actual) Date of First Enrollment: **2012/10/01**
- Target Sample Size: **12**
- Monocenter/Multicenter trial: **Monocenter trial**
- National/International: **National**

Inclusion Criteria

- Gender: **Both, male and female**
- Minimum Age: **18 Years**
- Maximum Age: **no maximum age**

Additional Inclusion Criteria

indication for 177Lu-DOTATATE therapy:
- well differenciated, metastasized neuroendocrine tumors or carcinoma, which overexpress somatostatin receptors subtyp 2 (positive pretherapeutic 68Ga-DOTA-TATE PET/CT) and which are not able to treat curative,
- meningiomas, which overexpress somatostatin receptors subtyp 2 and which are not able to treat with an alternative treatment.

pro DOTATATE therapy:
- progress of tumor, "firt line, second line therapy",
- metastasis, not local restricted to the liver,
- significant overexpression of somatostatin receptor subtyp 2,
- normal kidney function.

- able and willing to give informed consent

Exclusion criteria

- renal insufficiency, creatinine >1.5 mg/dl and/or GFR <60 ml/min, fixed disease of the efferent urinary tract
- myelosupression: thrombocytes <90tds/mycroliter, hemoglobin <8.0 g/dl, leucocytes <2.5 tds/mycroliter
- Karnofsky index <60%
- somatostatin receptor imaging: tumor-uptake < liver-uptake
- pregnancy

- relative contra-indication: proliferation index >20%

Addresses

- **Primary Sponsor**

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Sources of Monetary or Material Support

- **Institutional budget, no external funding (budget of sponsor/PI)**

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Status

- Recruitment Status: **Recruiting complete, follow-up continuing**
- Study Closing (LPLV): **[---]***

Trial Publications, Results and other documents

** This entry means the parameter is not applicable or has not been set.*

**** This entry means that data is not displayed due to insufficient data privacy clearing.*