Exploration of VEGF expression in paediatric high grade glioma and diffuse intrinsic pontine glioma using 89Zirconium-bevacizumab imaged by PET

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Determining VEGF expression in pHGG and DIPG using 89Zr-Bevacizumab

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Nervous system neoplasms malignant and unspecified NEC
Study type	Interventional

Summary

ID

NL-OMON38105

Source
ToetsingOnline

Brief title
89Zr-Bevacizumab PET in pHGG & DIPG

Condition

- Nervous system neoplasms malignant and unspecified NEC
- Nervous system neoplasms malignant and unspecified NEC

Synonym
brainstem tumor, high grade glioma

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Stichting Semmy

Intervention

Keyword: Bevacizumab, High grade glioma, PET, Zirconium

Outcome measures

Primary outcome

VEGF-expression measured by Standard Uptake Values of 89Zr-Bevacizumab in pHGG

and DIPG

Secondary outcome

- Optimal moment of scanning obtained by five patients with positive

89Zr-bevacizumab uptake

- Body biodistribution and dosimetry of 89Zr-bevacizumab

Study description

Background summary

Paediatric high grade gliomas (pHGG) including diffuse intrinsic pontine gliomas (DIPG) have a poor prognosis. pHGG highly express vascular endothelial growth factor (VEGF), which is involved in mitogenic, angiogenic, and permeability enhancing processes. The monoclonal antibody bevacizumab inhibits VEGF-A and showed efficacy in adult glioma and to a lesser extend in pHGG. Bevacizumab can be labelled to Zirconium-89 for drug distribution and non-invasive target expression studies imaged by PET. Zirconium-89 is a positron emitter with a long half-time which is preferable because of its safety, purity and stable binding to its antibody and relatively low costs. In adults, 89Zr-bevacizumab could be used safely in humans and was shown to visualise targets precisely. In our study, bevacizumab is microdosed at 1/100th of the therapeutic dose in pHGG and DIPG. PET-imaging of 89Zr-bevacizumab may help to select future patients more likely to respond to bevacizumab therapy.

Study objective

Determining VEGF expression in pHGG and DIPG using 89Zr-Bevacizumab

Study design

This a multicenter diagnostic trial. All patients receive 10 ml of 89-zirconium (18.5mbq)- bevacizumab (2mg) i.v.. 89Zr bevacizumab PET scans will be performed at 1, 72 and 144 hours post-injection (p.i). Each PET scan will be preceded by a low-dose CT. Following the CT, a 10 min static PET-CT scan will be performed covering the brain, followed by a whole-body PET scan (4 min per bed position, total duration circa 25 min) to determine the 89Zr-biodistribution. After defining the Volume of Interest by co-registration of a T1 MRI, tumor to background ratios and Standardized Uptake Values will be calculated. If the Zirconium-89 dose (18.5mbq) appears to be insufficient to obtain good quality images, the zirconium dose (without increasing the bevacizumab dose) can be increased up to 40 mbq in subsequent patients.

Intervention

89-Zr bevacizumab once

Study burden and risks

Risks: This is a diagnostic study in patients with a lethal disease. Bevacizumab, used as a diagnostic, is dosed 1/100th of the therapeutic dose (10mg/kg) and therefore no adverse events of bevacizumab are expected. All patients have been or will be irradiated, usually with a total dose of 54Gy. The radiation burden added by this study is therefore, negligible. Patients receive a total dose of 0.9 MBq/kg, 0.1 mg/kg 89Zr-bevacizumab, which results in an expected radiation dose of 20-45 mSv. An additional 3mSv will be added by the low dose CT scans for each whole body PET/CT examination. The total radiation burden of three whole body PET/CT examinations will be 29-50mSv. For comparison, the worldwide average background dose for a human being is about 2 mSv per year. In case the images in the first patient(s) appear to be of inferior quality, the zirconium-89 dose can be increased up to 37 Mbq. The total radiation burden will then be maximum 50mSv. A previous study in patients with head and neck cancer did not report any zirconium-related toxicity in 20 patients who received 89Zr-labeled anti-CD44v6 (a monoclonal antibody), followed by surgery.
In general, allergic reactions may occur at non-therapeutic doses and therefore patients will be monitored carefully for a few hours from time of injection. However, in several zirconium-89 studies including an ongoing UMCG 89Zr-bevacizumab study with more than 20 adult patients being enrolled so far, no allergic reactions were observed (personal communication dr. L. de Vries).

Burden: All participants receive an i.v. cannula and undergo three whole body PET scans in one week. They have to lay down quiet for 30 minutes for each scan. No anaesthesia will be used. Our standardised training program enables children from four years to undergo MRI without major problems. An advantage of PET is that the quality of the images is less influenced by small movements compared to MRI. To reduce the patient burden, we have chosen not do perform

blood collections, which is usual in adult PET studies.

Benefit: Subjects do not have a direct personal benefit from this diagnostic study, although they can be treated on an individual base with bevacizumab in case of a positive PET scan.

Group relatedness: We are certainly aware of this burden, but in our opinion, the scientific value of this project outweighs this concern, because selection of patients may lead to effective personalized treatment cancer and helps to prevent the administration of inactive drugs and the accompanying side effects in the future. Studies in pHGG are necessary since biology including receptor kinase expression clearly differs from adult HGG. These PET-labelling studies are not only applicable to children with HGG and DIPG, but in fact to all children with solid tumours.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)

Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

- DIPG (MRI confirmed, biopsy not required) after radiotherapy
- De novo biopsy proven HGG with minimal residual tumor of 5 mm in each dimension
- pHGG & DIPG patients with progressive disease after radiotherapy
- Age between 4 and 18 years
- Able to lay down quiet for 30 minutes

Exclusion criteria

- Chemotherapy or radiotherapy in the past two weeks
- Previous administration of bevacizumab or another anti-VEGF drug
- Known hypersensitivity against humanized monoclonal antibodies
- Neurofibromatosis type I

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	15-11-2011
Enrollment:	10
Type:	Actual

Ethics review

Approved WMO Date:	23-08-2011
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Not approved Date:	27-07-2012
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	11-02-2013
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 27519
Source: NTR
Title:

In other registers

Register	ID
CCMO	NL34922.000.11
OMON	NL-OMON27519