A Dose Escalation Phase I Study Of hrBMP4 Administrated Via Convection-Enhanced Delivery In Patients With Progressive And/Or Multiple Recurrent Glioblastoma Multiforme.

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Primary:To evaluate the feasibility and safety of intra-tumour and peri-tumour therapy with GMP hBMP4 in increasing doses in patients with progressive and/or multiple recurrent GBM, identify DLT, and to determine whether there is a maximum tolerated...

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

Summary

ID

NL-OMON46932

Source
ToetsingOnline

Brief title
Clinical study in patients with brain tumor, testing a new protein:hrBMP4

Condition

- Nervous system neoplasms malignant and unspecified NEC

Synonym
Glioblastoma Multiforme - braintumor

Research involving
Human

Sponsors and support

Primary sponsor: Stemgen
Source(s) of monetary or material Support: Stemgen

Intervention

Keyword: Braintumor, Glioblastoma, hrBMP4

Outcome measures

Primary outcome

The primary objective of this study will be to evaluate the feasibility and

safety of intra-tumour and peri-tumour therapy with GMP hBMP4 in increasing

doses in patients with progressive and/or multiple recurrent GBM, identify DLT,

and to determine whether there is a maximum tolerated dose (MTD).

Secondary outcome

secondary endpoints are: tumor response measured on MRI scans, pharmacokinetics

of hrBMP4 in blood and quality of life.

Study description

Background summary

Gliomas are the most common supratentorial primary brain tumour in adults and children. Malignant gliomas constitute at least 35% of all primary brain tumours and are the 3rd leading cause of death from cancer in persons 15 to 34 years. Despite advances in conventional treatments, the prognosis for most patients with gliomas remains poor. For patients with the most common form, glioblastoma multiforme, the median survival is approximately 1 year, and at most, only 5% of people will survive 5 years after diagnosis. In patients with recurrent GBM following conventional therapy, the median overall survival time is 25-27 weeks (Wong et al 1999 and Huncharek & Muscat 1998). This has led to an intensive search for alternatives.

Conventional treatment of malignant gliomas is based on surgery (whenever possible), and on therapies, such as radiotherapy and chemotherapy, which are

toxic to cells, primarily targeting cells that proliferate rapidly. However, despite advances in conventional treatments, the prognosis for most patients with gliomas remains poor.
The diminished efficacy seen in many such treatments is not related to the inability of the cytotoxic compounds to kill tumour cells but is more related to the sub-optimal dose given to patients in order to avoid systemic toxicity and to the induced resistance of tumour cells to these therapies.

Based on the ability of hrBMP4 to cause terminal differentiation of BTSCs without apparent toxicity, our underlying hypothesis is that hrBMP4 can be safely and effectively delivered into and around malignant glioma tissue by means of Convection Enhanced Delivery (CED) to deliver BMP4 into brain tissue, including tumours, allowing convective distribution of high drug concentrations over large volumes of the target tissue, while avoiding systemic toxicity (Bobo, et al., 1994) (Lieberman, Laske, Morrison, Bankiewicz, & Oldfield, 1995), making CED perfectly suited for delivery of BMP4 to recurrent GBM. As detailed above, infusion of hrBMP4 was able to extend hGBM-bearing mice survival, starting at the dosage of a total of 40 µg of protein delivered over two weeks. hrBMP4 can therefore severely lessen the growth of GBM tumours in vivo using technical settings similar to those proposed for human patients.

Study objective

Primary:
To evaluate the feasibility and safety of intra-tumour and peri-tumour therapy with GMP hBMP4 in increasing doses in patients with progressive and/or multiple recurrent GBM, identify DLT, and to determine whether there is a maximum tolerated dose (MTD)

Secondary:
* To assess the radiological response to GMP hrBMP4 following intra-tumour and interstitial administration by convection enhanced delivery (CED).
* To assess the systemic exposure to GMP hrBMP4 following intra-tumour l and interstitial administration by CED.

Study design

This multicentre, open-label, dose escalating, Phase I study will enrol approximately 18 patients with progressive and/or multiple recurrent GBM, who after failure of standard therapies will receive GMP hrBMP4 via intra-tumour and interstitial delivery by CED.
5 dose levels will be tested in a 3+3 design; one dose level will be assigned to a cohorts of 3 patients, if one patients develops an SAE another 3 patients in this dose level will be treated. If no SAEs occur the next dose level will be tested. If another SAE will occur this level will be considered as a DLT and the MTD will be determined as one dose level beneath this level.

Intervention

The intervention will consist of intratumoral slow delivery by CED of the study drug. For this the patient will be admitted during 6 days . In a surgical procedure under general anesthesia 3 catheters will be placed in and around the tumor and a needle biopsy will be performed, all using neuronavigational techniques.
After this the study drug will be infused in and around the tumor during 4 days with micro infusion pumps.

Study burden and risks

The clinical advantages in the use of hrBMP4 is an alternative approach to cytotoxic therapy based on inducing stem and progenitor cell differentiation, causing them to lose their stem and proliferative qualities as well as their tumour/initiating capacity.

It is believed the risks for patients treated with hrBMP4 in this Phase I study will be minimal for the following reasons: (1) hrBMP4 will be delivered directly to the tumour reducing systemic exposure to hrBMP4 and possible peripheral effects, (2) BMP2, which is a similar ligand as hrBMP4 that binds to the same receptor and has nearly identical actions on blocking proliferation of tumour cells (Lee et al, 2008) is FDA approved for peripheral human clinical use, (3) over expression of hrBMP4 in a rodent produced no changes in the number of neurons, myelination patterns or gross structural abnormalities (Gomes, Mehler, & Kessler, 2003), and (4) our published (Piccirillo et al, 2006) and unpublished pre-clinical data have found no toxicity related issues with infusion of up to 100 *g of hrBMP4 either subcutaneously or intracranially.

Patients will be admitted for 6 days in which a surgical procedure takes place and the study drug will be infused in and around the tumor by micro infusion pumps during 4 days. During the surgery 3 catheters will be placed in and around the tumor and a needle biopsy of the tumor will be taken. The risks of needle biopsy is well established in literature, it consists of approx 1 % of causing a bleeding, A number of bleedings, but not all maybe symptomatic causing neurological deficit, some of which may be permanent. Very rarely a bleeding may be fatal .
Infusion of studydrug into the brain may cause increased pressure leading to headache, worsening of existing neurological deficit or seizures. These are all treatable with corticosteroid medication. Mostly these symptoms are temporary, ceasing when infusion is ended. Our group was involved in another CED study in which 60 catheters were placed , without causing bleedings or tissue damage

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Patients at least 18 years of age with malignant glioma (WHO grade IV) who have undergone conventional treatment, including surgery (gross total resection or unintentional partial resection with residual tumour) or biopsy (with residual tumour), and/or radiation therapy, and/or chemotherapy, and have progressive and/or multiple recurrent GBM.

Exclusion criteria

Patients who had chemotherapy, radiotherapy or other anti-neoplastic therapy (within 4 weeks or 5x
half-life whichever is shorter) prior to study treatment or those who have not recovered from toxicity

to the last therapy. Patients in bad neurological condition, with a KPS lower than 70.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	11-07-2017
Enrollment:	9
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	hrBMP4
Generic name:	hrBMP4 (Recombinant Bone Morphogenic Protein-4)

Ethics review

Approved WMO Date:	25-07-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	17-05-2017
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	06-07-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-07-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2016-001761-92-NL
ClinicalTrials.gov	NCT02869243
CCMO	NL58347.078.16