A phase I/II trial of a conditionally replication-competent adenovirus (delta-24-rgd) administered by convection enhanced delivery in patients with recurrent glioblastoma multiforme

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

Summary

ID

NL-OMON35590

Source
ToetsingOnline

Brief title
n.a.

Condition

- Nervous system neoplasms malignant and unspecified NEC

Synonym
brain tumor, glioblastoma multiforme

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: ZonMw

Intervention

Keyword: adenovirus, gene therapy, glioblastoma

Outcome measures

Primary outcome

The safety and tolerability (defined as the Maximum Tolerated Dose (MTD)) of

Delte-24-RGD Adenovirus administered by Convection Enhanced Delivery to the

tumors and the surrounding infiltrated brain in patients with recurrent

Glioblastoma Multiforme

Secondary outcome

- Progression Free Survival (PFS)

- Overall Survival (OS)

- Tumor response rate in patients with recurring tumors amenable for surgical

resection and treated at the MTD

Study description

Background summary

Delta-24-RGD is the name of an experimental drug for the treatment of a specific type of brain tumor, glioblastoma multiforme (GBM). Delta-24-RGD is a virus and can be categorized to the group of adenoviruses. These virussee are well known and under normal circumstances they will cause harmless infections of the respiratory tract, like a cold and flu-like symptoms.

Viruses are very small particles which need a host cell to multiply themselves. Delta-24-RGD is an adenovirus which is modified in such a way that they specifically infect cells which contain so called integrines. These integrines

are expressed mainly on tumor cells. A second modification to this virus makes sure that the virus can only multiply itself in tumor cells, so normal cells will not be affected. These modifications will make the virus *tumor-selective*, and hardly able to destroy normal cells.

Thet Delta-24-RGD adenovirus will be administered directly during 2 to 3 consecutive days in the tumor and its surroundings through 3 or 4 temporarily implanted catheters, which are connected to an infusion pump containing the drug. It is aimed that the drug will spread very slowly in and around the tumor area, in order to reach as much tumor cells as possible. Subsequently, the tumor cells must be infected by Delta-24-RGD, which will lead to cell death.

Study objective

GBM is difficult to treat, due to the fact that tumor cells can move until several centimeters in the brain around the visible tumor location. these infiltrated cellscan not be removed by surgery and are resistant to chemotherapy and radiation. This new treatment method investigates if Delta-24-RGD can kill the tumor cells efficiently, and also if the method for administration through the catheters ensure that all tumor cells will be reached.

The primary objective of this study is to establish the maximum tolerated dose for Delta-24-RGD, and if Delta-24-RGD will have an effect on tumor growth. The effects of administartion of Delta-24-RGD on tht immunesystem will also be investigated.

Study design

A maximum of 42 patients will participate in this study. After surgical resection of the recurring tumor, or after a biopsy in case resection is not feasible, catheters will be placed and the patients will receive Delta-24-RGD infusion during 2 to 3 consecutive days. Patients will stay in the hospital for about 10 days, and will be examined subsequently at 2, 4, 12 weeks and then every 3 months after start of treatment. All planned visits will be completed after 1 year and the patient wil then be contacted every 6 months.

Intervention

Patients having a recurring tumor amenable for surgical resection will undergo debulking surgery first. Subsequently 4 catheters will be placed in and around the tumor area during a second surgical procedure within maximum 7 days after resection. During this operation, catheters will also be placed, which make it possible to take fluid and tissue samples from the brain at various time points after te operation. Both operations will take place under complete anaesthesia.

Patients having a recurring tumor not amenable for surgical resection will undergo one surgical procedure in which the tumor will be biopsied followed by catheter placement.

Study burden and risks

1. Complications due to administration of a virus in the brains could be an inflammatory reaction against the virus by activation of the immune system. Symptoms are flu and meningitis-like symptoms. These symptoms will in general decrease without treatment, but in very serious cases they could lead to neurological impairment or death.
2. Complications due to the extra operation needed to implant the catheters could occur. The risk of infection after implantation of the catheters increases significantly after 7 days; in this study the catheters will be removed after maximum 5 days. Implantation of the catheters may cause a bleeding; it is estimated that the chances for such a risk are less than 1%.
3. Brain tumor patients often present with symptoms and signs of increased intracranial pressure. Since Delta-24-RGD infusion is performed directly in the tumor area, there is an increased risk for development of edema. Furthermore, direct infusion of foreign drugs, such as Delta-24-RGD in the brains can cause an allergic reaction. The following symptoms could be observed: headache, nausea, dizziness, fever, seizures, sleepyness, bleedings, infection, increased intracranial pressure, impairment of neurological symptoms and in the most severe case a possible increased risk of death.
4. Because still not much is known about the possible riscs of Delta-24-RGD for siblings, both male and female participants with the potential to conceive a child should use safe preservatives during 3 months after start of infusion with Delta-24-RGD.

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

1.Patients with histologically proven primary Glioblastoma Multiforme (GBM) will be eligible for this protocol.
2.Patients must show unequivocal evidence for tumor recurrence or progression by MRI scan within 3 weeks prior to registration after failing prior resection (surgery or biopsy) and/ or chemo- and/or radiation therapy.
3.Recurring tumors must either be accessible for surgery, or , when not accessible for surgery meet the following criteria:
a. unifocal
b. midline shift * 0.5 cm
c. no radiological signs of uncal herniation
4.All recurring tumors must be restricted to one hemisphere, without signs of subependymal spreading.
5.Before start of virus treatment histological analysis of the resected, or biopsied tumor recurrence must confirm the diagnosis of GBM (based on frozen section).
6. Patients may or may not have had prior chemotherapy.
7. Patients must be able to read and understand the informed consent document and must sign and date the informed consent. Procedures to obtain such informed consent should be according to ICH-GCP, the local regulatory requirement and the rules followed at the institute.
8. Patients must be > 18 and < 75 years old.
9. Patients must have a Karnofsky performance status rating > 70 (Appendix 2).
10. Patients must have recovered from the toxic effects of prior therapy. For example, they must be at least two weeks after vincristine, 6 weeks after nitrosoureas, 3 weeks after procarbazine or temozolamide administration, and 6 weeks after radiation therapy.
11. If sexually active, patients must be willing to use barrier contraception for the duration of the study.
12. Patients must have adequate hepatic, renal and bone marrow function, defined as
• absolute neutrophil count (ANC) > 1,5* 109/L
• platelet count of > 100* 109/L

• ALT (SGPT), AST (SGOT) and Alkaline Phosphatase <= 2 times ULN
• total bilirubin <26 umol/l
• creatinine <1.5 times ULN
• urea (BUN) <1.5 times ULN

Exclusion criteria

1. Patients with active uncontrolled infection. Upper pulmonary infection and flu-like signs or presence of adenovirus in pre-treatment throat-swab or serum sample as determined by PCR. All patients must be afebrile (<38.0C) at the start of therapy.
2. Evidence of bleeding diathesis or use of anticoagulant medication that cannot be safely stopped.
3. Patients with systemic diseases or other unstable conditions which may be associated with unacceptable anesthetic/operative risk and/or which would not allow safe completion of this study protocol, e.g. uncontrolled seizures, steroid dependence.
4. Females who are pregnant, at risk of pregnancy, or breast feeding a baby during the study period.
5. Immune-compromised individuals and patients known to have HIV infection are excluded because of the potential risk of serious infection
6. Patients with other primary malignancy than GBM. However, patients with curatively treated carcinoma-in situ or basal cell carcinoma or patients who have been disease free for at least 2 years and not using any anti-cancer therapy, are eligible.

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):	16-06-2010
Enrollment:	42
Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	Genetic modified organism

Ethics review

Approved WMO Date:	27-10-2008
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-01-2009
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	01-02-2010
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-03-2010
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	26-09-2011
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	09-11-2011
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	

Date:	23-10-2013
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	29-10-2013
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

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2007-001104-21-NL
CCMO	NL24958.000.08